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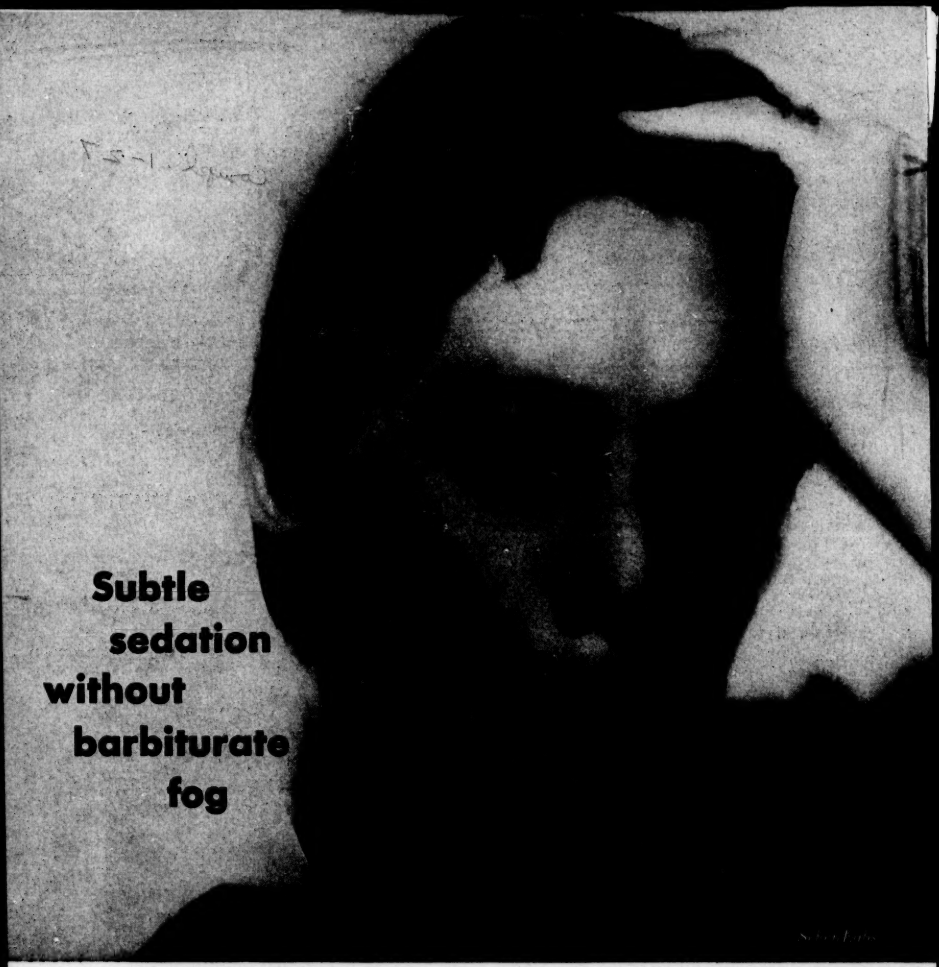

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PERSONNEL EXPOSURES ASSOCIATED WITH THE THERAPEUTIC USE OF RADIUM, RADON AND COBALT-60*

EGILDA DEAMICIS, S.B.,† AND RUSSELL F. COWING‡

BOSTON

BEFORE the protection problems of personnel exposed to radium, radon and cobalt-60 are considered it seems advisable to review some of the terminology that is generally used in conjunction with radioactive materials.

The term radioisotope is applied to a material that has exactly the same chemical properties as a nonradioactive substance, the difference being that the radioisotope has different physical properties in that it emits radiation, which may be in the form of either particles or rays or both, depending on the specific isotope involved. The unit of dose for a radioisotope is the millicurie, which is an accepted rate of disintegrations per second. Disintegrations per second implies that there is radiation coming off from the substance as particles or rays. Radium emits two kinds of radiation—beta particles and gamma rays, which are approximately a thousand times more penetrating than beta particles. Because the gamma rays associated with both radium and cobalt travel considerable distances in air a protection problem arises. Another term commonly associated with isotopes is half life. Radiocobalt has a half life of 5.3 years; this means that at the end of 5.3 years only half as many millicuries are present in the source. Radon has a half life of 3.85 days, and radium one of 1590 years.

PROTECTION PROCEDURE

In setting up protection procedure and in evaluating exposure one is concerned with the roentgens received in an interval of time. A roentgen is a definite measure of the quantity of radiation of x or gamma rays produced under certain conditions. The smaller unit, milliroentgen (mr), is equal to 1/1000th of a roentgen, or 1000 milliroentgens = 1 r. Exposure levels are frequently quoted in terms of milliroentgens per hour, per day or per week. The National Bureau of Standards[1] has recommended that the permissible dose for total body exposure to x or gamma radiation is 0.3 r, or 300 mr, per week measured in air. This dose may be received[2] at the rate of 50 mr per day or more rapidly, provided the weekly dose is not exceeded. The National Bureau of Standards[1] has also recommended that the permissible exposure to the hands and forearms be set at 1500 mr per week at the basal layer of the epidermis; anyone obtaining isotopes—for example, cobalt-60—from the Atomic Energy Commission is bound to observe these levels.[3,4]

To be assured that the permissible level of radiation is not exceeded or, if it is exceeded, that it is known, all personnel working with radioactive materials should wear film badges,[1] which contain a specially developed dental film that, when processed in compliance with the manufacturer's specifications, show varying degrees of blackening depending on the exposure received. The blackening is related to exposure by means of comparison with standard curves[5] developed for the isotope in question. It is not known until after the film is developed whether or not the permissible exposure is exceeded; the film does indicate a check on conditions and the fact that perhaps changes should be made in technic. In view of this it is judicious to plan all procedures and evaluate all technics and exposure for carrying out a particular problem.

A consideration of the various methods or combination of methods that one may employ in keeping the personnel exposure below the permissible level should be discussed. First of all, from a point source of radiation, the quantity of gamma radiation varies inversely as the square of the distance. For example, if from a cobalt-60 source one measures 100 mr at a distance of 60 cm., at 120 cm. the measurement is 25

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mr, which one can obtain mathematically as follows:

$$\text{mr} = \frac{60 \times 60}{120 \times 120}$$

Distance, therefore, may be employed as a safety factor. If the procedure to prepare a cobalt applicator requires 30 minutes of work and the dosage rate is 100 mr per hour the exposure received would be 50 mr. By means of the distance and the time factor the radiation level could be reduced. Even with these factors, it is not always possible to bring the radiation level to the permissible dose, and protective material, such as lead, needs to be employed. The amount of lead required will vary with the particular isotope, its millicurie level, the energy of its radiation and the maximum time involved for the procedure.

A certain thickness of lead that will reduce the quantity of radiation to half its initial value is called the half-value layer[5]; it is 0.47 inches (1.2 cm.) for radium and 0.55 inches (1.4 cm.) for cobalt-60. By knowing these values one can calculate the thickness of lead wall required in a carrier used for transporting radium, cobalt-60 or radon seeds and also the thickness necessary for a barrier to protect personnel during the loading of applicators and cleaning of needles. To determine how much lead is needed to reduce the radiation level it is necessary to know the quantity of radiation emitted from a given source. These radiation levels should be measured with an accurately calibrated ionization chamber, but it is important to calculate how much radiation is involved in a particular procedure.

It has been established that a point source of radium filtered with 0.5 mm. of platinum emits at 1 cm. from the source 8.4 r per hour per millicurie or milligram, and cobalt-60, when it is unfiltered, emits 13.5 r per hour per millicurie.[6] With these values in mind the protection problems associated with cobalt-60 such as that employed in a Massachusetts hospital can be considered. All the cobalt-60 that the hospital owns—a total of 10 applicators of 17 millicuries each—is stored in a lead carrier having a thickness on all sides of 2.8 cm. of lead and a 15-cm. handle. This storage box is permanently located in a locked, lead storage vault of such thickness that less than 6 milliroentgens per hour are emitted 25 cm. from it. It is assumed that 6 applicators of cobalt-60, each containing 17 millicuries, are to be used in the treatment of cancer of the cervix. All the cobalt-60 in the lead storage carrier is transported to the preparation room and set behind a lead protective barrier. It would be reasonable to assume that 2 minutes is required for a nurse to transport the cobalt-60 to the lead barrier. A calculation of the exposure to the nurse's hands involves the following factors:

One millicurie of cobalt-60 as a point source emits 13.5 r per hour at 1 cm. from the source.

One roentgen = 1000 mr.

Two minutes of time (2/60th of an hour) is assumed for the procedure.

Each capsule contains 17 millicuries, and there are 10 capsules in the storage carrier.

Source-to-hand distance is 15 cm.

Inverse-square law is applicable for the calculation of the exposure to the hands.

The lead on the carrier is equivalent to 2 half-value layers and decreases the radiation by a fourth.

Exposure to the hands is as follows:

$$13.5 \times 1000 \times \frac{2}{60} \times 17 \times 10 \times \frac{1}{15 \times 15} \times \frac{1}{4} = 85 \text{ mr.}$$

The exposure to the trunk level assumed to be at 30 cm. from the source is 21 mr.

The cobalt-60 applicators required for the treatment are transferred from the storage carrier to a lead sterilizing box with a 15-cm. handle and lead walls 2.5 cm. thick (approximately 2 half-value layers of lead). Total body exposure to the nurse resulting from this transference will be about 3 mr because the lead protective barrier, 5.7 cm. thick on all sides, affords 4 half-value layers of protection, and the time for this duty is not greater than 3 minutes. The exposure of the nurse's hands will be higher than the total body exposure because the nurse employing instruments giving a 25-cm. source-to-hand distance receives no hand protection from the lead barrier. In the process of transferring the 6 applicators from one container to another the nurse is exposed to 10 applicators of 17 millicuries each. The calculation of the exposure is as follows:

$$13.5 \times 1000 \times \frac{3}{60} \times 17 \times 10 \times \frac{1}{25 \times 25} = 184 \text{ mr.}$$

The cobalt-60 is next transported to the sterilizing room. If the transportation time is 2 minutes the exposure to the nurse's hands is 51 mr and that to her body 13 mr. If someone is in the sterilizing room during the process he is at least 100 cm. from the source, and, if the sterilizing process requires 20 minutes, the total body exposure for the 20-minute period is as follows:

$$13.5 \times 1000 \times \frac{20}{60} \times 17 \times 6 \times \frac{1}{100 \times 100} \times \frac{1}{4} = 11.5 \text{ mr.}$$

The cobalt-60 is transfered in a 2-minute period from the sterilizing room to the operating room. The exposure to the nurse's hands would be 51 mr and that to her body 13 mr. The total exposure to the nurse's hands from all procedures would be 371 mr and that to her body 50 mr. (It will be recalled that the permissible weekly hand exposure is 1500 mr and the permissible total body exposure is 300 mr.)

The surgeon prepares the cobalt applicators for placement in the patient. If he spends 15 minutes in preparation at a distance of 30 cm. his hands will receive the following dose:

$$13.5 \times 1000 \times \frac{15}{60} \times 17 \times 6 \times \frac{1}{30 \times 30} = 382 \text{ mr.}$$

The exposure to his body at 45 cm. from the source is as follows:

$$13.5 \times 1000 \times \frac{15}{60} \times 17 \times 6 \times \frac{1}{45 \times 45} = 171 \text{ mr.}$$

Because the weekly permissible dose is being approached and the surgeon receives an additional exposure from placement of the applicators in the patient the loading procedure should be carried out behind a lead barrier with a minimum thickness of 1 half-value layer of lead. The use of this barrier reduces the exposure to the surgeon's body to 86 mr. If the surgeon requires 5 minutes to place the applicators in the patient, 57 mr will be delivered to his trunk, and a dose of 127 mr will be delivered to his hands. The total exposure received by the surgeon in all procedures is 143 mr to his total body and 509 mr to his hands. Both these values are below the weekly permissible dose.

The cobalt-60 remains in the patient for the period of treatment. During the treatment period of 3 days floor-duty nurses are exposed to a certain amount of radiation while caring for the patient. It is not likely that the same nurse cares for the patient for these 3 days. Also, it should be pointed out that the source of radiation is in the cervix and that the amount of time a nurse spends close to the source is minimal. For an example, on the assumption that during one 8-hour work period the nurse spends 10 minutes at 60 cm. from the source and one hour at about 90 cm. from the patient, performing other duties, the exposure to her body is 64 mr from the 60-cm. and 104 mr from the 90-cm. vicinity, or 168 mr total. On the basis of these figures the same nurse would exceed the permissible weekly level if she cared for the patient for the 3-day period. A rotation of three nurses would prevent this overexposure provided that they were not assigned to any other radiation cases during the week.

While the patient is being treated the question of visitors arises. Actually, visitors are not occupational workers,[2] and they may never again be exposed to radiation except for medical purposes. On the basis of an exposure of 1 hour each day for 3 days and on the assumption that the distance from the source to the visitor is 90 cm. the body exposure is 400 mr, which is 100 mr above the permissible level for radiation workers.

At the end of the treatment time a physician removes the cobalt from the patient and places the active material in a transportation box with 1.5 cm. of lead (1 half-value layer) on all sides and with a 30-cm. handle. If he requires 5 minutes for the removal procedure and if he employs instruments giving 20 cm. of distance to his hands, the exposure will be

$$13.5 \times 1000 \times \frac{5}{60} \times 17 \times 6 \times \frac{1}{20 \times 20} = 288 \text{ mr},$$

and that to his body will be 46 mr.

The cobalt-60 is then transported back to the preparation room and is placed behind the lead protective barrier, where it is stored until the cleaning of the applicators is carried out. The exposure involved in a transportation time of 5 minutes and at a distance of 30 cm. is

$$13.5 \times 1000 \times \frac{5}{60} \times 17 \times 6 \times \frac{1}{30 \times 30} \times \frac{1}{2} = 64 \text{ mr}$$

to the hands and the same amount to the body.

All cleaning of applicators should be carried out behind the lead protective barrier, which is 5.7 cm. thick and affords 4 half-value layers of protection to the entire body. The applicators are handled one at a time, and forceps giving a 25-cm. source-to-hand distance are employed. Those applicators not being handled are kept in the lead storage carrier, which affords an additional half-value-layer of protection to the body. A cleaning time of 3.5 minutes is necessary for each applicator; the exposure from one applicator is 21.5 mr, and that from the six applicators 129 mr. There is an added exposure from the lead carrier containing needles waiting to be cleaned. At a 50-cm. distance from the storage carrier 66 mr is delivered to the hands. Therefore, the total exposure in cleaning the six needles is 195 mr; this is less than the permissible hand dose for a day — 250 mr. The total body exposure to the nurse is very low, only about 6 mr, because her body is behind the lead shield and is at a distance of 60 cm. from the source.

TABLE 1. *Summary of Exposures.*

DUTY	PERSONNEL	RADIATION EXPOSURE	
		HANDS mr	TOTAL BODY mr
Transportation & duties from vault location to operating room	Nurse 1	371	50
Loading & placement of applicators in patient	Surgeon	509	143* 288†
Nursing care	Nurse 2		168
	Nurse 3		168
	Nurse 4		168
Removal of cobalt-60	Physician	288	46
Transportation (return to lead shield)	Nurse 5	64	64
Cleaning of needles	Nurse 6	195	6

*With use of lead shield.
†Without use of lead shield.

Table 1 is a compilation of the exposures that have been considered in a particular case of treatment of cancer of the cervix.

As stated above, it is essential to make such calculations to be assured that personnel will not be overexposed. However, it is equally important that, once procedures have been evaluated, the actual radiation involved in the procedures should be checked with an ionization chamber, which will give a meter reading in terms of mr per hour. These values may then be interpreted in terms of actual working times.

The problem of calculating exposures for radium is the same as that for cobalt-60 except that, instead of 13.5 r per hour per centimeter from a 1-millicurie point source, radium filtered with 0.5 mm. of platinum gives off 8.4 r per hour per milligram, and this figure

is used in the calculations. Before a protection problem with radium needles is considered problems associated with radon seeds are discussed.

Radon itself emits only alpha rays, which are cut out by the 0.3-mm. gold-tubing filter on the radon seeds. However, radon is in equilibrium with radium and decays to radium B and radium C, which emit both beta and gamma rays. The 0.3-mm. gold-tubing on the seeds cuts out most of the beta particles so that, essentially, the protection problem is one related to gamma rays. Radon, fortunately, has a short half life, 3.85 days, and, hence, decays rapidly so that the intensity of radiation falls off rapidly. The following analysis of the use of radon seed as employed at the New England Deaconess Hospital considers 20 seeds of 1.5 millicuries each.

Transportation

The carrier should be of sufficient thickness to keep the hand exposure below the permissible level. With a 2.5-cm. lead thickness and a 10-minute handling time the weekly permissible level of radiation is not exceeded.

Sterilization of Seeds in Alcohol

Since instruments giving 13 to 20 cm. of distance are used and the process of dropping seeds into the alcohol takes less than 1 minute, the exposure involved in this process is 26 mr to the hands.

Loading Seeds into Trocars

An 11-cm. forceps is used, with a 5-cm. hand-to-seed distance. The time for loading 20 seeds is about 7 minutes. Most of the time figures for handling the seeds are high; this adds a safety factor in protection. The hand exposure is 58 mr, and the total body exposure 38 cm. from the sources is about 1 mr.

Physician Inserting Seeds into Patient

The physician's hands are about 13 cm. from the seeds, his body is about 38 cm. from the seeds, and his total working time is 20 minutes. The exposure to his hands is 490 mr, and that to his body 59 mr.

Scrub Nurse Attending Physician

The nurse is about 38 cm. from the seeds, and she works with the physician for 20 minutes; her exposure is 59 mr.

If the patient is hospitalized the exposure to the floor nurses is halved in 3.85 days (half life of radon) and decreases 16.6 per cent each day.

Typical Exposure in a Year

As one last exposure problem an analysis made at New England Deaconess Hospital of exposure to the radium nurse over a year's period is presented. There are 2 radium nurses, who handle all cases (they are not concerned with any other isotope work). The exposure is calculated at the trunk level and for 20 3-mg. needles filtered with 0.5 mm. of platinum. Various nursing duties include threading of needles, transportation of the needles to and from the lead safe, to the sterilizing room and to the operating room, sterilization of needles, attendance when physician inserts and removes needles and cleaning of needles. The exposures from these duties total 71 mr. With the addition of a 25 per cent safety factor the nurse receives per case about 90 mr. From the radium report covering January 1 to December 31, 1952, all cases, including canceled ones, add up to 32, involving a total of 1685 mg., or 52.5 mg. as an average for each case. Assuming 263 actual working days per year (all holidays are not taken) the permissible dose for the year is 13,150 mr. Since the original problem of exposure from 20 3-mg. needles (60 mg. total) resulted in 90-mr exposure, the exposure from 52.5 mg., the average value of radium in each case, is 80 mr.

For 32 cases the exposure is 2560 mr. This value is 20 per cent of the yearly permissible dose of radiation. Since canceled cases were included, and also since there are 2 radium nurses employed, it may be seen that the exposure is well below the permissible level.

References

1. U. S. Department of Commerce, National Bureau of Standards. *Safe Handling of Radioactive Isotopes. (Handbook 42.)* 30 pp. Washington, D. C.: Government Printing Office, 1949.
2. Glasser, O., Quimby, E. H., Taylor, L. S., and Weatherwax, J. L. *Physical Foundations of Radiology.* Second edition. 581 pp. New York: Hoeber, 1952. P. 424.
3. U. S. Atomic Energy Commission. Isotopes Division. *Isotopes. (Catalog and Price List No. 4.)* 75 pp. Oak Ridge, Tennessee: U. S. Atomic Energy Commission, March, 1951. Pp. 53 and 54.
4. U. S. Atomic Energy Commission. Application for Radioisotope Procurement, Form AEC-313.
5. Cowing, R. F., and Spalding, C. K. Photographic effect of various radiations on special dental packets. *Radiology* 52:423-426, 1949.
6. Glasser, O., Quimby, E. H., Taylor, L. S., and Weatherwax, J. L. *Physical Foundations of Radiology.* Second edition. 581 pp. New York: Hoeber, 1952. P. 399.

THE PROBABLE SYSTEMIC NATURE OF MIKULICZ'S DISEASE AND ITS RELATION TO SJÖGREN'S SYNDROME*

WINFIELD S. MORGAN, M.D.†

BOSTON

IN 1892 Mikulicz[1] described a case of benign, asymptomatic, symmetric enlargement of the lacrimal and salivary glands. Microscopical examination of excised portions of the glands disclosed atrophy of the acinar parenchyma and diffuse replacement by lymphoid tissue. Apparently, this was the first report of its kind given much attention in the literature, and in time the condition received the name "Mikulicz's disease." In the years that followed this became a very confused subject. Many cases manifesting enlargement of the salivary or lacrimal glands were diagnosed as Mikulicz's disease with little attention to the histopathology. Later, it became apparent that bilateral enlargement of these glands was merely a syndrome that might be produced by leukemia, malignant lymphoma, sarcoidosis, tuberculosis or other diseases that tended to be generalized. There were occasional cases, however, that did not fit well recognized pathologic entities, and eventually such cases were classified as Mikulicz's disease of unknown etiology in which the true histopathology was not certain in contrast to Mikulicz's syndrome, caused by leukemia, sarcoidosis and other diseases whose pathological nature had been more clearly defined.

In a recent study by Morgan and Castleman[2] a detailed investigation of the diseases causing enlargement of the salivary and lacrimal glands resulted in the microscopical finding of a distinctive pathologic process in 18 cases. From a consideration of the clinical and pathological aspects of these 18 cases, it was believed that they best fit the original description by Mikulicz. Clinical review revealed that the disease was usually characterized by chronic, painless enlargement of one or more of the salivary or lacrimal glands. Follow-up studies for as long as twenty years indicated that the disease was benign and not associated with glandular enlargement elsewhere in the body. In contrast to Mikulicz's contention that the disease always involved the lacrimal glands it was found to be more commonly confined to the salivary glands. At variance with the long-held belief that the glandular involvement in Mikulicz's disease is always bilateral, slightly more than half the patients had only unilateral enlargement; yet the picture microscopically was the same in both groups. Fifteen of the 18 patients were women, all of whom were thirty-five years to sixty-two years of age, with a majority in the fifth and sixth decades. Grossly, the typical picture presented by the involved gland was one of diffuse enlargement with preservation of lobular architecture. Microscopically, the disease was characterized by a gradual lymphocytic infiltration that replaced the glandular parenchyma concomitantly with an intraductal proliferation of myoepithelial and epithelial cells. The latter change resulted in obliteration of the ductal lumens and the formation of solid cell masses ("epimyoepithelial islands") scattered throughout a lymphoid stroma (Fig. 1).

During the course of this study, a number of articles by Sjögren[3-13] were encountered describing a condition well known to ophthalmologists. In the complete form, Sjögren's syndrome, or the sicca syndrome, as it is sometimes called, is said to consist of decreased or absent lacrimation associated with a dry, filamentary keratitis and conjunctivitis (keratoconjunctivitis sicca), dryness and atrophy of the mucous membranes of the nose, mouth and throat (rhinostomatopharyngolaryngitis sicca), enlargement of the parotid glands and chronic polyarthritis. Many cases, however, show only two of these features. The condition has an insidious onset, and its course may be marked by remissions, although more often it is progressive. It is chronic and confined almost exclusively to women over forty years of age. One of Sjögren's[8] articles contained a photomicrograph of the parotid gland (Fig. 2) that demonstrated infiltration by lymphoid tissue as well as the characteristic ductal alteration observed in the 18 cases of Mikulicz's disease.

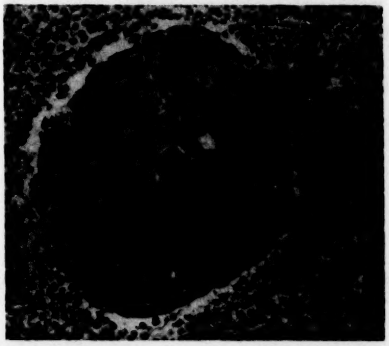

FIGURE 1. *Typical Field from 1 of the 18 Cases of Mikulicz's Disease, Showing an Epimyoepithelial Island (Altered Duct), with Hyaline Deposition Surrounded by Lymphoid Tissue (Reproduced from Morgan and Castleman[2] with the Permission of the Publishers).*

*From the Department of Pathology, Massachusetts General Hospital. Presented in part at the fiftieth annual meeting of the American Association of Pathologists and Bacteriologists, St. Louis, April 2, 1953.

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In view of this finding it was decided to determine what relation, if any, existed between the cases considered to be Mikulicz's disease and those described by Sjögren. The problem was approached in three ways: permission was obtained to review Sjögren's original microscopical slides; the clinical records of the 18 cases of Mikulicz's disease were re-examined for the presence of other lesions, in addition to enlarged salivary glands, that are features of Sjögren's syndrome; and cases of Sjögren's syndrome reported in the literature, supplemented by 5 more observed in this hospital, were studied for similarities to the 18 cases previously interpreted as Mikulicz's disease.

Review of Sjögren's Microscopical Material

It was found that in most of the cases in Sjögren's series the microscopical sections of the salivary glands

Figure 2. Photomicrograph of a Parotid Gland, Showing Changes Similar to those Described in Figure 2 (Reproduced from Sjögren' with the Permission of the Publishers).

revealed all the features previously recorded in the 18 cases of Mikulicz's disease. Relatively few sections of the lacrimal glands were available for comparative study. These exhibited infiltration and replacement of the parenchyma by lymphoid tissue, but in none were the typical ductal changes observed; it is possible, however, that they were present elsewhere in the gland since the sections represented biopsy material.

Clinical Reinvestigation of 18 Cases of Mikulicz's Disease

Since a majority of the patients were of middle age or older, they represented a nearly ideal group in which the occurrence of features of Sjögren's syndrome throughout their lifetimes might be sought. In this regard, it is well known that one component of Sjögren's syndrome might antedate the development of another by years; and very frequently the diagnosis is made when only two are observed.

It was found that two patients had clinical evidence of keratoconjunctivitis sicca (Table 1). In Case 4 both lacrimal glands were enlarged, with microscopical changes similar to those observed in the salivary glands in other cases of the series, including the presence of epimyoepithelial islands. Case 5 had definitely diminished tearing, as indicated by a positive Schirmer test in addition to filamentary keratitis. Case 1 had recurrent bilateral conjunctivitis, and Case 16 had a persistent, cheesy discharge from both eyes without conjunctivitis. Neither patient, however, was adequately studied; therefore, the classification of the type of ocular disease remains indefinite.

Few of the patients with rhinostomatopharyngolaryngitis were examined carefully enough to permit definite conclusions concerning the incidence of gross changes in the mucous membranes of the nose, mouth and throat, and in no case was tissue available for study. However, 2 patients (Cases 1 and 5) had prominent buccal glands and dryness of the oral mucosa; 6 others complained of inadequate saliva. This last symptom was present in patients in whom involvement of only one salivary gland was apparent as well as in those with multiglandular disease. Therefore, in some of the cases dryness of the mouth could not be wholly attributed to disease of the larger salivary glands and may have been due to abnormal changes in the buccal mucosa.

Five patients had a history of arthritis. In 2 (Cases 6 and 15) this was of the rheumatoid type. Case 7, a seventy-year-old man, had had arthritis "for many years" but had never been examined for this complaint and had died by the time the study was begun. Although the arthritis in this case must be classified as indeterminate it seems most likely from information subsequently obtained that it was rheumatoid. The remaining 2 patients were also not available for further investigation, but were considered to have findings of degenerative joint disease at the time of admission for treatment of salivary-gland enlargement.

One patient (Case 5), a forty-seven-year-old woman who had had bilateral parotid-gland enlargement for ten years, died of disseminated lupus erythematosus. A fifteen-year-old boy (Case 18), the only patient under thirty-five years of age, had had rheumatic fever several years before admission and had continued to have an elevated sedimentation rate up until the time of entry.

Of the entire series of 18 patients 9 had one or more of the other features of Sjögren's syndrome in addition to the disease of the salivary glands.

Review of Cases of Sjögren's Syndrome

Practically all the cases of Sjögren's syndrome in the literature have been reported by ophthalmologists. Accordingly, interest has tended to center on the ocular manifestations, and most papers have consisted of studies of patients who had keratoconjunctivitis as the primary complaint. Table 2 summarizes the findings in several series of cases of Sjögren's syndrome as well as in 5 additional cases observed in this hospital.

The last illustrate the clinical nature of Sjögren's syndrome, and since only 1 has previously been reported, these 5 cases are described here briefly. The first patient was a thirty-eight-year-old woman who, on admission to the hospital for treatment of rheumatoid arthritis of three and a half years' duration, was also found to have keratoconjunctivitis sicca, dryness and atrophy of the oral and pharyngeal mucosa and parotid-gland enlargement. A second case was that of a sixty-year-old woman who had had rheumatoid arthritis for twenty-two years; at the time of admission for a variety of vague complaints, filamentary keratitis and xerostomia were discovered. The third patient, a fifty-seven-year-old woman with a history of rheumatoid arthritis for thirty-five years, was found to have keratoconjunctivitis sicca and dryness of the mouth when admitted to the hospital for evaluation of the arthritis. The fourth was a woman who had recovered from thrombocytopenic purpura at the age of eighteen after splenectomy, and keratoconjunctivitis sicca, bilateral salivary-gland enlargement and dryness of the mouth had developed seven years later. The fifth patient was first seen in this hospital in 1929 at the age of fifty-seven, when she gave a history of burning of the eyes with discharge for ten years. On ophthalmologic examination typical signs of filamentary keratitis were present. Three years later she was found to have parotid-gland enlargement, with dryness of the mouth, and several years later rheumatoid arthritis developed. At the time of the

TABLE 1. *Data in 18 Cases of Mikulicz's Disease.**

CASE NO.	HOSPITAL AND UNIT NO.†	AGE ON ADMISSION	SEX	KNOWN DURATION OF ENLARGEMENT OF SALIVARY OR LACRIMAL GLAND	GLAND AFFECTED	PERTINENT CLINICAL HISTORY OTHER THAN ENLARGEMENT OF SALIVARY OR LACRIMAL GLAND	FOLLOW-UP PERIOD
		yr.		yr.			yr.
1	MGH 654319	35	F	1	Both parotid & both submaxillary glands	Mucous glands of mouth enlarged; recurrent conjunctivitis.	7
2	BMH Ch7246	61	F	12	Both parotid & both submaxillary glands	Dryness of mouth	7
3	MGH 347218	62	F	½	Both parotid & both submaxillary glands	Dryness of mouth; probable degenerative arthritis.	7
4	MGH 78205	39	F	5	Both lacrimal glands	Keratoconjunctivitis sicca	3½
5	MGH 292008	47	F	1	Both parotid glands	Keratoconjunctivitis sicca; mucous glands of mouth enlarged; dryness of mouth; death from disseminated lupus erythematosus 2 mo. after admission.	(Autopsy)
6	MGH 639608	55	F	11	Both parotid glands	Dryness of mouth; rheumatoid arthritis; death from infectious hepatitis about 2 yr. after 1st admission.	(Autopsy)
7	NEDH 42:1355	70	M	1	Lt. parotid & lt. submaxillary glands	Arthritis (indeterminate type) for many years	7
8	MGH 301975	59	F	1	Lt. parotid & lt. submaxillary glands	None: patient had severe arteriosclerosis and died of circulatory collapse shortly after excision of salivary glands.	(Autopsy)
9	MGH 781786	37	F	5/12	Rt. parotid gland	None	1/12
10	BCH 780284	39	M	1	Rt. parotid gland	None	18
11	MGH 8855	48	F	1	Rt. parotid gland	None	20
12	MGH 582057	47	F	1½	Lt. parotid gland	None	5½
13	NEDH 8149	50	F	10	Lt. parotid gland	None	4
14	MGH 18682	56	F	½	Lt. parotid gland	Dryness of mouth	18
15‡	MGH 130611	37	F	5/6	Lt. parotid gland	Dryness of mouth; rheumatoid arthritis.	15
16	MGH 622014	40	F	1/6	Lt. parotid gland	Idiopathic retinal arteritis with bilateral partial blindness	17
17	MGH 35-527	69	F	2	Lt. parotid gland	Dryness of mouth & throat; probably degenerative arthritis.	10
18	MGH 59958	15	M	1	Lt. submaxillary gland	Rheumatic fever 5 yr. previously; continued elevated sedimentation rate.	5½

*The case numbers conform in number sequence with those in a previous report.[3]

†Abbreviations for hospitals: MGH (Massachusetts General Hospital); NEDH (New England Deaconess Hospital); BCH (Boston City Hospital); BMH (Booth Memorial Hospital).

‡Twelve yr. after excision of left parotid gland readmitted because of enlargement of right parotid gland, which was also excised, revealing identical changes microscopically.

first admission neither lacrimal gland was enlarged; however, a biopsy of one lacrimal gland was taken. Microscopical examination revealed changes identical to those found in the 18 cases of Mikulicz's disease.

The variation in distribution of involvement in these cases is an impressive one, and is considered most significant in the light of the conclusions that follow. A majority of the patients in these reports were women of middle age in whom the disease had been chronic. In no case was associated lacrimal-gland enlargement recorded.

Discussion

The foregoing comparative study has disclosed that Mikulicz's disease, as found previously in 18 cases, and Sjögren's syndrome are similar from the following standpoints: their clinical nature and course; the tendency to occur in middle age; the preponderant incidence in women; the identical histologic findings in the salivary and lacrimal glands; and the coexistence in both groups of similar associated lesions, in addition to disease in the salivary glands, such as keratoconjunctivitis sicca, xerostomia and rheumatoid arthritis. This degree of similarity suggests that the two conditions are related, if not actually the same pathologic process.

Although Mikulicz himself examined only 1 patient with the symptom complex that was to bear his name and although many cases have been reported and classified as Mikulicz's disease[20-22] in which involvement was limited to the salivary glands, subsequent writers have perpetuated the belief that enlargement of lacrimal glands is a required part of Mikulicz's disease. The absence of lacrimal-gland enlargement in cases of Sjögren's syndrome has been used by some authors[18,23] as an important point in distinguishing otherwise similar and confusing cases. It will be observed that, in the present study, only 1 of the 18 patients previously considered to have Mikulicz's disease had enlarged lacrimal glands. Microscopically, however, this tissue exhibited the same pathological changes observed in the salivary glands in other patients, who apparently did not have lacrimal-gland involvement. Similarly, although the lacrimal gland was not enlarged in the case classified as Sjögren's syndrome, the biopsy specimen revealed identical changes histologically. Therefore, although the available microscopical material of the lacrimal glands in these cases is limited, the present evidence supports the conclusion that the lacrimal glands are less frequently enlarged in Mikulicz's disease than previous writers have believed. The presence or absence of one physical finding, such as enlargement of lacrimal glands, should not be used as a basis for dividing such cases into two entities.

It appears, from the review of the literature on Sjögren's syndrome given earlier, that although the incidence of salivary-gland enlargement, dryness of the mouth and arthritis is variable, the feature common to these cases is keratoconjunctivitis sicca. This should not be taken to mean, however, that the ocular involvement is necessarily more frequent or important than the other components of the syndrome. All these studies were made by ophthalmologists, who clearly approached the problem from the standpoint of keratoconjunctivitis. Conversely, then, it seems likely that in the past reports of Mikulicz's disease similar emphasis was given to the enlargement of the salivary and lacrimal glands to the exclusion of coexisting lesions, such as keratoconjunctivitis sicca. That this is almost certainly so is more than suggested by the fact that, in a significant number of the past case reports of Mikulicz's disease,[20,22,24-26] incidental note is made that the patient had conjunctivitis or arthritis.

The observation, apparently first made by Houwer,[27] much extended by Sjögren and later confirmed by others,[14-18,28,29] that rheumatoid arthritis was a frequent concomitant finding in cases of keratoconjunctivitis sicca was an important contribution; it perhaps provides a lead to the cause of the changes in the salivary and lacrimal glands. It challenges the conclu-

Table 2. *Findings in Cases of Sjögren's Syndrome.**

Source	No. of Cases	Sex		Patients with Salivary-Gland Enlargement	Patients with Dryness of Mouth	Patients with Arthritis
		Males	Females			
Sjögren[9]	19	6	13	2	9	13
Beetham[14]	9	0	9	3	7	3
Bruce[15]	14	2	12	6	9	6
Coverdale[16]	5	1	4	3	5	?2
Gifford et al.[17]	33	5	28	2	15	11
MacLean[18]	3	0	3	2	3	2
Lutman & Favata[29]	2	0	2	2	2	0
Mass. Gen. Hosp. & Mass. Eye & Ear Infirmary	5†	0	5	3	5	4

*All patients had keratoconjunctivitis sicca.
†One of these, patient M.S. from Beetham's series, is included here since additional symptoms developed after his report.

sion drawn in older studies of Mikulicz's disease that some obscure localized infection produces the glandular alterations, and strongly suggests the possibility of a systemic origin.

Since there is considerable evidence that an intimate relation exists between rheumatoid arthritis and certain other generalized diseases such as disseminated lupus erythematosus and periarteritis nodosa, it is interesting that 1 of the 18 patients died of disseminated lupus erythematosus. Recently, Shearn and Pirofsky,[30] in a comprehensive clinical study of 34 cases of disseminated lupus erythematosus, noted that 3 patients had a history of chronic enlargement of the salivary glands; Shearn[31] subsequently encountered still another patient with similar findings. In none of these cases, unfortunately, was it possible to explain the cause of salivary-gland enlargement since tissue was not available for microscopical study. Other clinical reviews of these diseases[32-35,38-40] have not been of sufficient detail to indicate the degree to which chronic disease of the salivary or lacrimal glands might have been a concomitant finding. Of 60 patients with disseminated lupus erythematosus and 46 with periarteritis studied in this hospital the only patient in whom chronic salivary-gland enlargement was recorded was the woman with disseminated lupus erythematosus in the present series. This investigation of the frequency of chronic disease of the salivary or lacrimal glands in association with the other members of the so-called connective-tissue diseases, gives only slight suggestion that the incidence might be increased in disseminated lupus erythematosus. This result may not, however, indicate the true frequency since in many of the separate case reports, as well as in the two large series reviewed by Montgomery[41] and Montgomery and McCreight,[42] no mention was made of the condition of these glands.

Since Sjögren's syndrome is uncommon and in many cases only two components may be present, with perhaps only one of these prominent, it is suggested that if more is to be learned about this condition, there will have to be greater co-operation between the several services of the hospital to which these patients will be admitted. Accordingly, the surgeon will see most of the patients who manifest swelling of the salivary glands, the ophthalmologist those with keratoconjunctivitis sicca or enlargement of the lacrimal gland, the rhinolaryngologist those complaining of dryness of the nose, mouth or throat, and the internist, especially the rheumatologist, those in whom arthritis is the predominant symptom. It is very likely that only when an additional large number of patients have received careful study will knowledge concerning Sjögren's syndrome be placed on firmer ground. Finally, further detailed histologic studies, especially in patients examined at autopsy, are required.

Summary and Conclusions

In a comparative histologic study of 18 previously reported cases of so-called Mikulicz's disease and the microscopical material from the original series of Sjögren's syndrome, the pathological changes in the salivary glands were found to be identical.

A re-examination of the clinical records of the 18 patients previously considered to have Mikulicz's disease disclosed that a significant number had other components of Sjögren's syndrome such as keratoconjunctivitis sicca, xerostomia and rheumatoid arthritis.

Conversely, a study of cases classified as Sjögren's syndrome revealed that the incidence of the several components of Sjögren's syndrome was extremely variable, and in addition, many of the patients had chronic enlargement of the salivary glands, one of the prominent features of Mikulicz's disease.

The condition characterized by chronic enlargement of the salivary or lacrimal glands, which in the past has been called Mikulicz's disease, may be a less highly developed variant of a larger symptom complex, Sjögren's syndrome.

Because of the high incidence of rheumatoid arthritis in Sjögren's syndrome it is possible that the pathologic process in the salivary or lacrimal glands is similar and of systemic origin.

Since this article was submitted for publication I have had the opportunity of studying the microscopical sections of the salivary and lacrimal glands in the case of Sjögren's syndrome reported by Ellman, Weber and Goodier.[46] To my knowledge this is the only report in the literature describing the complete autopsy findings in a case of the syndrome. Examination of the microscopical material revealed the same characteristic changes previously found in the 18 cases of Mikulicz's disease—namely, lymphocytic infiltration, atrophy of glandular parenchyma and ductal alterations with the formation of epimyoepithelial islands.

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References

1. Mikulicz, J. Concerning peculiar symmetrical disease of lacrymal and salivary glands. *M. Classics* **2**:185-186, 1937-38.
2. Morgan, W. S., and Castleman, B. Clinicopathologic study of Mikulicz's disease. *Am. J. Path.* **29**:471-503, 1953.
3. Sjögren, H. Zur Kenntnis der Keratoconjunctivitis sicca (Keratitis filiformis bei Hypofunktion der Tranendrusen). *Acta ophth.* **11** (Supp. 2): 1-151, 1933.
4. *Idem.* Zur Kenntnis der Keratoconjunctivitis sicca. II. Allgemeine Symptomatologie und Ätiologie. *Acta ophth.* **13**:1-39, 1935.
5. *Idem.* Zur Kenntnis der Keratoconjunctivitis sicca. III. Mikroskopische Veränderungen der Nasendrüsen. *Acta ophth.* **13**:40-45, 1935.
6. *Idem.* Dry keratoconjunctivitis as partial symptom of larger symptom complex. *Nord. med. tidskr.* **9**:953-960, 1935.
7. *Idem.* Further studies of keratoconjunctivitis sicca. *Acta ophth.* **15**: 319, 1937.
8. *Idem.* Zur Kenntnis der Keratoconjunctivitis sicca. IV. Mikroskopische Untersuchungen über das Initialstadium der Drüsenveränderungen. *Acta ophth.* **16**:70-79, 1938.
9. *Idem.* Zur Kenntnis der Keratoconjunctivitis sicca. V. Augenveränderungen nach Exstirpation der Tränendrüse Behandlung. *Acta ophth.* **16**:80-88, 1938.
10. *Idem.* Zur Kenntnis der Keratoconjunctivitis sicca. VI. Das Siccasyndrom und ähnliche Zustände: Dacryo-Sialo-Adenopathia atrophicans. *Acta ophth.* **18**:369-382, 1940.
11. *Idem.* Keratoconjunctivitis sicca. In *Modern Trends in Ophthalmology*. 690 pp. Edited by F. Ridley and A. Sorsby. London: Butterworth, 1940. Pp. 403-413.
12. *Idem. A New Conception of Keratoconjunctivitis Sicca (Keratitis Filiformis in Hypofunction of the Lachrymal Glands)*. 152 pp. Sydney, Australia: Australasian Medical Publishing Company, 1943.
13. *Idem.* Some problems concerning keratoconjunctivitis sicca and sicca syndrome. *Acta ophth.* **29**:33-47, 1951.

14. Beetham, W. P. Filamentary keratitis. *Tr. Am. Ophth. Soc.* **33**: 413-435, 1935.
15. Bruce, G. M. Keratoconjunctivitis sicca. *Arch. Ophth. Soc.* **26**:945-964, 1941.
16. Coverdale, H. Some unusual cases of Sjögren's syndrome. *Brit. J. Ophth.* **32**:669-673, 1948.
17. Gifford, S. R., Puntenney, I., and Bellows, J. Keratoconjunctivitis sicca. *Arch. Ophth.* **30**:207-216, 1943.
18. MacLean, A. L. Sjögren's syndrome. *Bull. Johns Hopkins Hosp.* **76**:179-191, 1945.
19. Lutman, F. C., and Favata, B. V. Keratoconjunctivitis sicca and buccogiossopharyngitis sicca with enlargement of parotid glands: report of 2 cases of Sjögren's syndrome, with pathologic study of lacrimal gland and parotid glands in one case. *Arch. ophth.* **35** (N.S.): 227-240, 1946.
20. Howard, C. P. Mikulicz's disease and allied conditions. *Internat. Clin.* **1**:30-63, 1909.
21. Smith, J. F., and Bump, W. S. Lymphoid hyperplasia of lacrimal and salivary glands: Mikulicz's disease. *Ann. Surg.* **88**:91-97, 1928.
22. Godwin, J. T. Benign lymphoepithelial lesion of parotid gland. *Cancer* **5**:1089-1103, 1952.
23. Riva, G. Zur Kenntnis des Sjögrenschen Syndrome. *Schweiz. med. Wchnschr.* **28**:376-381, 1945.
24. Leucutia, T., and Price, A. E. Mikulicz's disease and Mikulicz's syndrome. *Am. J. Roentgenol.* **24**:491-515, 1930.
25. Lehman, J. A., and Leaman, W. G., Jr. Mikulicz's disease. *Internat. Clin.* **3**:105-111, 1940.
26. Jackson, A. S. Mikulicz's disease: report on patient treated with penicillin. *Am. J. Surg.* **68**:358-363, 1945.
27. Houwer, M. Filamentary keratitis. *Tr. Ophth. Soc. U. Kingdom* **47**:88-99, 1927.
28. Godfredsen, E. Relation between Sjögren's disease: Plummer-Vinson syndrome and ariboflavinosis. *Acta ophth.* **25**:95-109, 1947.
29. Henderson, J. W. Keratoconjunctivitis sicca. *Am. J. Ophth.* **33**:197-223, 1950.
30. Shearn, M. A., and Pirofsky, B. Disseminated lupus erythematosus. *Arch. Int. Med.* **90**:790-807, 1952.
31. Shearn, M. A. Personal communication.
32. C'axton, H. E., Jr., and Krause, L. A. M. Acute lupus erythematosus disseminatus. *Ann. Int. Med.* **19**:843-872, 1943.
33. Shaffer, B., James, G. W., Scully, J. P., and Pillsbury, D. M. Systemic lupus erythematosus. *Am. J. M. Sc.* **221**:314-318, 1951.
34. Guion, C. M., and Adams, E. C. Six autopsied cases of disseminated lupus erythematosus. *Am. J. M. Sc.* **205**:33-41, 1943.
35. Cannon, A. B. Treatment of lupus erythematosus disseminatus by internal administration of iodine. *Arch. Dermat. & Syph.* **51**:26-31, 1945.
36. Banowitch, M. M., Polayes, S. H., and Charet, R. Periarteritis nodosa: report of 5 cases. *Ann. Int. Med.* **16**:1149-1179, 1942.
37. McCall, M., and Pennock, J. W. Periarteritis nodosa: our present knowledge of the disease. *Ann. Int. Med.* **21**:628-637, 1944.
38. Diaz-Rivera, R. S., and Miller, A. J. Periarteritis nodosa: clinicopathological analysis of 7 cases. *Ann. Int. Med.* **24**:420-443, 1946.
39. Harris, A. W., Lynch, G. W., and O'Hare, J. P. Periarteritis nodosa. *Arch. Int. Med.* **63**:1163-1182, 1939.
40. Spiegel, R. Clinical aspects of periarteritis nodosa. *Arch. Int. Med.* **88**:893-1040, 1936.
41. Montgomery, H. Disseminate lupus erythematosus. In *Oxford Medicine.* Vol. IV. Part I. Edited by H. A. Christian. New York: Oxford University Press, 1939. Chap. 1-C. P. 44(41).
42. Montgomery, H., and McCreight, W. G. Disseminate lupus erythematosus. *Arch. Dermat. & Syph.* **68**:356-372, 1949.
43. Ellman, P., Weber, F. P., and Goodier, T. E. W. Contribution to pathology of Sjögren's disease. *Quart. J. Med.* **20**:33-42, 1951.

OBSTRUCTIVE JAUNDICE DUE TO BULLET IN HEPATIC DUCT*

Report of a Case after a Latent Period of Nine Years

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THE presence of a foreign body in the extrahepatic biliary tract is extremely infrequent judging from the paucity of reports in the medical literature.[1-11] Having recently been confronted by the problem of obstructive jaundice developing several years after a wound, we believe that the case, together with its diagnostic and pathogenetic aspects, merits reporting. Previously reported cases are presented in Table 1.

CASE REPORT

J.D., a 29-year-old man, was admitted to the hospital on December 2, 1953. During combat activity in 1944 he received several gunshot wounds of the right lateral and posterior aspects of the chest. Surgical operation was performed immediately; the postoperative course was uneventful. The patient was told that one of the bullets had entered the liver.

These historical statements were confirmed by review of his Army medical record. On the day after the injury a thoracotomy was done; the diaphragm was sutured, and a bullet was removed from the right lung. A laparotomy was also performed, and a pack was placed in the liver wound and brought out through a stab wound in the flank. No wound of exit was found in the lower surface of the liver. The foreign body (bullet) was left in the liver. The patient was discharged from military service in 1945 with the following diagnoses: wound, gunshot, machine, penetrating, right side of the chest and abdomen with a point of entry in the right posterior axillary line, 8 cm. below the axilla continuing through the diaphragm into the liver; hemothorax, right; and foreign body, bullet, right lobe of liver. X-ray examination in February, 1945, disclosed an area of metallic density below the right leaf of the diaphragm. Unfortunately, this film was not available for review.

The patient had no specific complaints until 12 to 14 months before entry, when he began to notice aching, nonradiating pain in the region of the left hypochondrium, occurring at any time of the day or night and unrelated to the ingestion of food or to defecation. Anorexia and frequent episodes of vomiting were present during this period. He had observed that his urine periodically became darker than usual during the 2-year period before he entered the hospital. Generalized pruritus began 2 months before admission, and scleral icterus was noted shortly thereafter. He had lost 46 pounds during the previous year. He had been having 2 softer than normal stools daily for 2 months.

The patient had undergone a diagnostic study elsewhere 1 year previously, when the gall bladder could not be visualized. At cholecystography performed 1 month before entry nonvisualization was again reported.

The positive physical findings were icterus of the scleras and skin and mild epigastric tenderness. Examination was otherwise negative.

The pertinent laboratory findings are summarized in Tables 2 and 3.

Roentgenographic examinations disclosed resection of the 9th right rib posteriorly and blunting of the right costophrenic angle. A scout film of the abdomen revealed a 3-cm. radiopaque shadow just below the right leaf of the diaphragm whose shape was consistent with that of a bullet (Fig. 1). Cholecystography, which was attempted twice with 6 and 10 tablets of Telepaque respectively, resulted in nonvisualization each time. Examination of the upper gastrointestinal tract showed what appeared to be an extrinsic pressure defect along the superior border of the duodenal bulb and what was interpreted as representing a distended gall bladder; barium-enema examination revealed a normal colon.

Microscopical study of the sediment of material obtained by duodenal drainage demonstrated no calcium bilirubinate pigment, cholesterol crystals or tumor cells. The stools were light tan and mushy.

The preoperative clinical impression was extrahepatic biliary obstruction, probably secondary to chronic relapsing

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pancreatitis. The presence of the bullet was regarded as an incidental finding particularly since its position was well above the region of the common bile duct.

The patient was transferred to the surgical service; operation was performed on the 28th hospital day. The common bile duct was small but thicker than normal. There were numerous lymph nodes in the region of the common duct. The gall bladder was distended, and its walls were somewhat thicker than normal. The common and hepatic ducts were probed, and a metallic tinkle was elicited as the probe was inserted into the right hepatic duct. The bullet was impacted in the right hepatic duct at a point just proximal to the point of exit of the duct from the liver. The liver was normal in appearance. A bullet was removed from the hepatic duct. For the purpose of obtaining adequate exposure during the operation a cholecystectomy was performed. A T tube was inserted into the common bile duct.

Inspection revealed a metallic fragment measuring approximately 3.5 cm. in length and 1.2 cm. in diameter (Fig. 2). There was some distortion of the usual conical shape; the surface had the color of corroded brass. The gall bladder was edematous and thick and contained no calculi; histologic examination disclosed extensive cellular fibrosis and slight infiltration by lymphocytes. One lymph node showed hyperplasia. The pathological diagnoses were chronic cholecystitis and reactive lymph node.

The postoperative course was uneventful. Jaundice subsided, and the stools became darker. The liver profile showed several abnormalities before discharge on the 22d postoperative day. Cholangiography performed on the 18th day after operation demonstrated adequate filling of the biliary tree and prompt spill into the duodenum; however, the left hepatic duct appeared somewhat dilated. The patient was sent home with the T tube in place and with instructions to return later so that the tube could be removed.

TABLE 1. *Previous Reports of Foreign Bodies in the Biliary Tract.*

SOURCE	YEAR	FOREIGN BODY	SITE	COMMENT
Oppel[1]	1926	Surgical swab	Common duct	4 mo. after cholecystectomy
Fedoroff[2]	1930	Portion of T tube	Common duct	3 yr. after operation
Eichelter[3]	1931	Cotton fibers	Common duct	15 mo. after operation
Toland[4]	1933	Cotton gauze	Common duct	4 mo. after operation
Crawford & Stewart[5]	1939	Hemostat blade	Hepatic duct	7 yr. after cholecystectomy
Bowen[6]	1941	Fragment of catheter	Common duct	4 yr. after appendectomy
Lemierre & Pollet[7]	1927	Spoon handle	Common duct	Swallowed by insane woman
Goldhan[8]	1930	Copper bullet	Cystic duct	14 yr. after shooting
Cooke[9]	1932	Wire	Common duct	No history of surgery or injury
Hurt[10]	1947	Mortar fragment	Common duct	6 mo. after initial injury
Thorek[11]	1951	Rubber tubing	Common duct	25 yr. after cholecystectomy
Hebert & Swarts	1954	Machine-gun bullet	Right hepatic duct	9 yr. after injury

DISCUSSION

From a clinical point of view, although it was apparent that this patient had extrahepatic biliary-tract obstruction, the differential diagnosis was difficult. The presence of mild, intermittent, obstructive jaundice and left-upper-quadrant pain in a young man, with associated repeated failure to visualize a gall bladder that was apparently distended, strongly suggested the diagnosis of chronic relapsing pancreatitis. Although steatorrhea occurs in biliary-tract obstruction it is usually not associated with increased frequency of defecation or mushy stools. Repeatedly low values for serum amylase have been reported in chronic pancreatitis, and we did not consider this finding incompatible with that diagnosis. However, intravenous glucose tolerance tests were within normal

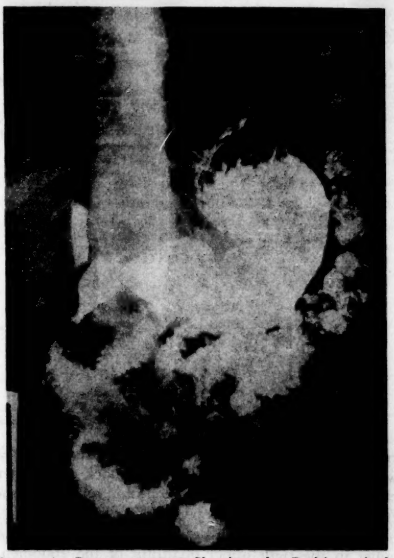


FIGURE 1. *Roentgenogram, Showing the Position of the Bullet in Relation to the Duodenum. Note the location well above the area of the common duct.*

FIGURE 2. *Photograph of the Machine-Gun Bullet Removed from the Hepatic Duct.*

limits, a finding that would have been exceptional in a patient with extensive destruction of the pancreas. There was no evidence of invasion or displacement of the duodenum by a neoplastic process in the pancreas. The absence of cholesterol crystals and bilirubinate pigment in a patient with choledocholithiasis would be most unusual. Hence, for lack of a better choice, it seemed wise to make chronic relapsing pancreatitis the working preoperative diagnosis.

Table 2. *Pertinent Laboratory Data.*

Date	Harrison Spot Test	Urinary Urobilinogen *dilution*	Serum Bilirubin *mg./100 cc.*	Bromsulfalein Retention %	Cephalin Flocculation	Thymol Turbidity *units*	Alkaline Phosphatase *Bodansky units*	Total Cholesterol *mg./100 cc.*
Dec. 3	+++	1:128	3.30		++	1.25	5.60	340
Dec. 7								
Dec. 10	+++	1:16	2.89		+	1.25	19.95	255
Dec. 16	+++	1:8	3.20		++	1.25	16.50	315
Dec. 18					+			
Jan. 2			5.42		+		5.25	
Jan. 6								
Jan. 7*								
Jan. 11			3.10		++	2.0	9.80	
Jan. 18			2.10		+++			
Jan. 26		1:4	1.65	12	++	1.5	10.75	167

*Day of operation.

Although we were well aware of the presence of a bullet in the right upper quadrant of the abdomen, we discounted its importance in view of its position far above and to the right of the position normally occupied by the common bile duct. In addition it seemed extremely unlikely that this patient could have spent nine years of his life without symptoms while he harbored a large-caliber bullet in his common bile duct.

It is interesting that in 7 of the 11 cases of foreign bodies in the biliary tract previously reported the objects had apparently been inadvertently introduced during earlier laparotomies.[1-6,11] It is equally interesting that in the only other 2 reported cases resulting from gunshot wounds, the projectiles were discovered six months and fourteen years later.[8,10] Only 1 other case of hepatic-duct obstruction by a foreign body has been reported; this was manifested by painless obstructive jaundice.[5] In Goldhan's[8] case the bullet was found in the cystic duct and, as one would have expected, produced only pain. A mortar fragment was removed from the common duct of Hurt's[10] patient six months after the initial injury, which involved the same region as that affected in our patient; here, as in our case, the fragment had been assumed to be deep in the substance of the liver.

Table 3. *Other Laboratory Data.*

Date	Prothrombin Time *sec.*	Serum Albumin *gm./100 cc.*	Serum Globulin *gm./100 cc.*	Nonprotein Nitrogen *mg./100 cc.*	Red-Cell Count *x10⁶*	White-Cell Count *x10³*	Hemoglobin *gm./100 cc.*	Serum Amylase *Somogyi units*	Fecal Fat *% dry wt.*
Dec. 3	14	4.0	3.3	31	4.56	11.5	13.0	25	
Dec. 7								31	
Dec. 10	13	3.8	3.7					20	
Dec. 16	15	4.2	3.3		4.22	8.6	12.0		35
Dec. 18								32	42
Jan. 2	15				4.33	14.0	12.8		
Jan. 6								31	
Jan. 7*									
Jan. 11	14	3.7	3.4						
Jan. 18	14	3.5	4.0						
Jan. 26	14	3.6	3.9						

*Day of operation.

Considering the number of wounds incurred during

recent wars, one wonders why this phenomenon has not been observed more frequently. The course of events in patients who had had no previous biliary-tract surgery and in whom there was a long asymptomatic interval suggests, although it does not prove, that the foreign bodies had migrated into the biliary tract.

Summary and Conclusions

A case of hepatic-duct obstruction nine years after a gunshot wound is reported.

The literature regarding the presence of foreign bodies in the biliary tract is briefly reviewed.

It is suggested that in some cases, including the one reported, bodies may migrate into the biliary tract during a variable period after the initial injury.

References

1. Oppel, W. A. Über chirurgische Misserfolge, insbesondere einer Fall von Durchwanderung eines Fremdkörpers aus der Bauchhöhle in den unverletzten Ductus choledochus. *Zentralbl. f. chir.* **53**:889, 1926.
2. Fedoroff, S. P. Drainrohr im Choledochus 5½ Jahre lang. *Zentralbl. f. chir.* **57**:657-662, 1930.
3. Eichelter, G. Drainagedochtfaden als Choledochus-fremdkörper Rezidivoperation. *Zentralbl. f. chir.* **58**:674-676, 1931.
4. Toland, C. G. Foreign bodies in biliary tract. *Ann. Surg.* **98**:904-908, 1933.
5. Crawford, B. L., and Stewart, H. L. Foreign body in hepatic ducts producing obstructive jaundice of seven years' duration with internal biliary fistula. *Am. J. Clin. Path.* **9**:353-360, 1939.
6. Bowen, F. H. Foreign bodies in biliary tract: report of case with tabular review of literature. *Arch. Surg.* **43**:458-461, 1941.
7. Lemierre, A., and Pollet, L. Suppuration hépatique diffuse consécutive à la pénétration d'un manche de cuiller dans le cholédoque chez une aliénée. *Bull. et mém. Soc. méd. d. hôp. de Paris* **51**: 241-244, 1927.
8. Goldhan, H. Steckschuss im Ductus cysticus. *Zentralbl. f. chir.* **57**:2664-2666, 1930.
9. Cooke, R. G. Foreign body in common bile duct. *Brit. M. J.* **1**: 840, 1932.
10. Hurt, R. L. Penetrating chest wound with lodgement of foreign body in common bile duct. *Brit. J. Surg.* **34**:429, 1947.
11. Thorek, M. Foreign bodies in hepatic ducts: review of literature. *J. Internat. Coll. Surg.* **15**:624-627, 1951.

INSULIN-RESISTANT DIABETES AFTER TOTAL PANCREATECTOMY*

Report of a Case

Bessie Dituri, M.D.†

PHILADELPHIA

CONTRARY to speculation diabetes mellitus that follows total pancreatectomy in man is relatively mild. In the absence of infection or other complications the requirement for insulin is usually stable and ranges from 20 to 40 units daily. There is relatively little tendency to spontaneous ketosis and coma, but insulin sensitivity has been a frequent problem in management. The marked contrast of these findings with those in many cases of naturally occurring diabetes mellitus has stimulated consideration of factors besides lack of insulin that produce hyperglycemia and ketosis and require large doses of insulin for correction.

In the following case, which is unique, as far as I know, diabetes mellitus appeared for the first time after total pancreatectomy. Large doses of insulin did not prevent hyperglycemia or glycosuria, and there was a tendency to rapid development of ketosis when insulin was withheld.

Case Report

H. A., a 50-year-old man weighing 145 pounds, was admitted to Temple University Hospital on April 21, 1953, because of mild epigastric pain and malaise of 5 weeks' and jaundice of 1 week's duration. On May 6 a total pancreatectomy was performed, together with splenectomy, duodenectomy and partial gastrectomy because of a diagnosis of carcinoma involving the entire pancreas. Multiple histologic sections revealed only chronic pancreatitis.

Immediately after operation no insulin was required, perhaps because of lack of adequate intake of food. After the 1st week insulin became necessary, and the patient was taking 20 units of protamine zinc insulin daily when he was discharged from the hospital. His weight on discharge was about 110 pounds. Attempts to control frequent and bulky stools were made by oral administration of pancreatic extract.

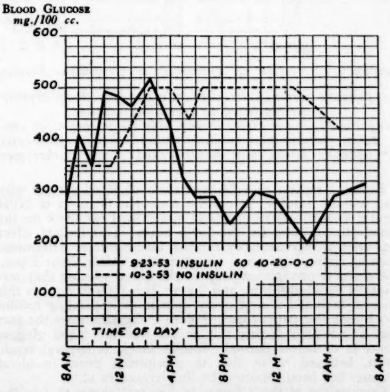


Figure 1. *Twenty-Four-Hour Blood Glucose Curve (Capillary Blood) with and without Insulin.*

This problem was never completely solved, but the number and the size of stools diminished. Because of the well known loss of large amounts of food in the stool food intake was increased to 3000 calories daily, composed of 350 gm. of carbohydrate, 120 gm. of protein and 110 gm. of fat. Despite the large intake of food he has been unable to regain his preoperative weight, and at present weighs only 125 pounds.

*From the service of Dr. L. A. Soloff, Temple University Hospital.
†Resident in medicine, Temple University Hospital.

After discharge from the hospital the dosage of insulin had to be increased gradually. At first, the increased requirement was attributed to a rise in intake of food, but later it was observed that, with a constant diet and constant weight, the present average dose of 180 units daily had to be given. Even this large amount of insulin was inadequate to control either the hyperglycemia or the glycosuria. The urine specimen collected at 11 a.m. constantly contained a large amount of glucose, and that at 4 p.m. usually contained a slight to moderate amount of glucose. The fasting blood sugar ranged between 140 and over 200 mg. per 100 cc. of blood. Various changes in the amount, type and time of injection of insulin and intake of food failed to abolish glycosuria. Much larger doses of insulin caused symptoms of hypoglycemia late in the evening. For these reasons the patient was readmitted to Temple University Hospital for study and for further attempts at standardization of insulin dosage.

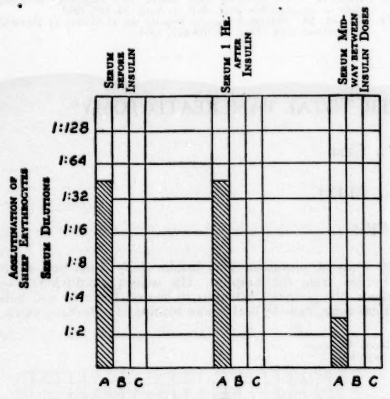


FIGURE 2. *Detection of Antibodies to Crystalline Insulin.*

A=patient's serum plus saline solution plus sheep erythrocytes sensitized to crystalline insulin.
B=patient's serum preincubated with 10 microgm. of crystalline insulin plus insulin-sensitized sheep erythrocytes.
C=patient's serum plus nonsensitized sheep erythrocytes.

Figure 1 represents a 24-hour study of blood glucose with and without insulin. It can be seen that 60 units of NPH insulin and 40 units of regular insulin had no effect on the blood glucose level for the 1st 6 hours. This lack of effect was verified repeatedly by random blood glucose determinations at appropriate times on other days. After about 2 p.m. there was a precipitous drop in the blood glucose that terminated between 8 p.m. and 2 a.m. It is interesting that this interval included almost every episode of impending insulin shock that this patient had. Figure 1 also illustrates the fact that at no time during this period was the blood glucose down to or below normal. Insulin shock at hyperglycemic levels, believed to be due to precipitous drops in blood glucose, has been reported by Sunderman et al.[1]

Comparison of the 2 curves of Figure 1 shows that in the absence of insulin there was no significant difference in the concentration of blood glucose from 8 a.m. to 2 p.m. but that a great difference appeared only after 2 p.m. During the 24 hours without insulin the patient lost 9 pounds and became obviously dehydrated, and ketonuria developed. For this reason further experimental observations involving withholding of insulin were not regarded as justifiable.

The possibility of the presence of antibodies to insulin was kindly investigated by Edward R. Arquilla,[2] of the Department of Anatomy and Microbiology, Western Reserve University School of Medicine.

Serum samples were collected 1 hour before and 1 hour after the morning dose of insulin and also approximately halfway between daily doses of insulin on a day when a total of 150 units of insulin was taken. Figure 2 is a graphic representation of the findings reported by Arquilla. It is of interest that there is an apparent correlation between fluctuations of the level of blood glucose and the concentration of antibody (Fig. 3). Free antibody is highest in the morning, when there is little response of the blood glucose level to insulin, and lowest in the evening, when the blood glucose has fallen to its lowest level.

DISCUSSION

Diabetes mellitus after total pancreatectomy has been described well over thirty times since the inception of radical pancreatic surgery a little over ten years ago. The data in 26 patients who survived the procedure for more than a month are listed in Tables 1 and 2. In these cases, not including the case reported above, only 2 patients required more than 40 units of insulin daily. Both cases were complicated by infection (pulmonary tuberculosis in 1 and cholangitis in the other). The others all required between 10 and 40 units a day. Moreover, insulin sensitivity is not uncommon. Clagett's patient (case reported by Waugh et al.[4]) died in insulin shock two and a half months after operation. In Marraffino's[15] patient in-

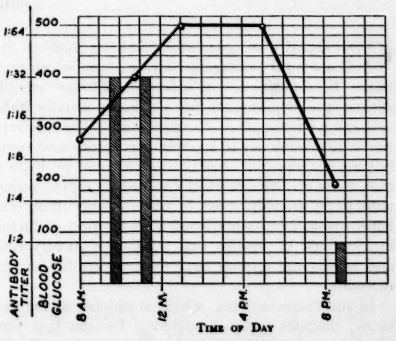


FIGURE 3. *Comparison of Blood Glucose Curve and Antibody Titer.*

sulin shock developed on the first day of normal oral feeding, 30 units of regular insulin having been given. In 1 of the patients of Shay and his associates[9] (a fifty-eight-year-old man) insulin shock occurred three and eighteen months after operation, and the patient died of intractable insulin shock. For this reason Bernard and Touraine[21] prefer hyperglycemia to normoglycemia in this type of case. Sensitivity to insulin may be due to the absence of the anti-insulin factor (hyperglycemic-glycogenolytic factor) supplied by the alpha cells of the pancreas.[22]

Insulin resistance has not been described previously in surgical diabetes. Root[23] defined resistance as a daily requirement of over 200 units in the absence of

ketosis. Davidson and Eddleman[24] collected a large number of reports, including that of an adolescent girl cited by Smelo.[25] This patient led an active normal life while requiring an average of 850 units of insulin daily and having a maximum twenty-four-hour requirement of 5000 units on a day when there were no known complications of her diabetes.

TABLE 1. *Data in Cases of Benign Pancreatic Disease.*

SOURCE	AGE	SEX	COMPLICATIONS	DIABETES BEFORE OPERATION	AVERAGE DAILY INSULIN REQUIREMENT
	yr.				units
Chronic pancreatitis:					
Whipple[2]	26	F	Far-advanced tuberculosis	No	30 80*
Waugh et al.[4]	39	F	None	No	38
Chapman[5]	58	M	None	No	None
Mazingarbe et al.[6]	57	M	None	No	40
Gourevitch & Whitfield[7]	55	M	Cholangitis for 1 yr.	No	50*
Cattell & Warren[8]	35	F	None	No	18
Shay et al.[9]	62	F	None	No	30
Owens[10]	59	M	Jejunal ulcer	No	35
Diturit	50	M	None	No	180
Hyperinsulinism:					
Priestley et al.[11]	49	F	None	No	30
Waugh et al.[4]	36	F	None	No	32

*Daily requirement with infection.
†Case reported in this communication.

Although the patient in the case reported above does not take 200 or more units of insulin daily he is insulin resistant in comparison to the others with

TABLE 2. *Data in Cases of Malignant Pancreatic Disease.*

SOURCE	AGE	SEX	METASTASES	DIABETES BEFORE OPERATION	AVERAGE DAILY INSULIN REQUIREMENT
	yr.				units
Carcinoma:					
Fallis & Szilagyi[12]	40	M	Yes	No	40
Fallis & Szilagyi[12]	57	F	No	Yes (8 yr.)	30
Fallis & Szilagyi[12]	60	F	No	Yes (15 yr.)	10
Brunschwig et al.[13]	53	M	Yes	Yes	40
Waugh et al.[4]	50	M	Yes	Yes	40
Lynch & Rosenberg[14]	50	M	No	No	27
Marraffino[15]	65	M	Yes	No	15
Warren[16]	65	F	Yes	No	30
Greenfield & Sanders[17]	58	M	Yes	Yes	40
Mazingarbe et al.[6]	65	M	Yes	Yes	20
Shay et al.[9]	58	M	No	Yes	35
Cattell & Warren[8]	49	M	No	No	10
Dubost et al.[18]	60	M	No	No	40
Sarcoma:					
Feather & Kuhn[19]	29	M	Yes	No	20
Nardi[20]	33	M	Yes	No	20

total pancreatectomy described. In addition the diabetes is not strictly controlled at present since a marked glycosuria occurs daily at 11 a.m., and a mild to moderate glycosuria occurs on some days at 3 p.m.

Insulin resistance may be placed in four possible classifications: infection and ketosis; hormonal,[26] including that due to the pancreatic hyperglycemic-glycogenolytic factor (alpha-cell hormone),[22] thyroxin, some adrenocortical hormones and anterior pituitary hormone[27]; enzymatic (theoretical possibility of circulating enzyme in blood that inactivates insulin—"insulinase"); and immunologic (antigen-antibody mechanism).

The patient described above has had no infection, and there is no evidence of thyrotoxicosis or adrenal or pituitary dysfunction. The factor of pancreatic hyperglycemia has been excluded by surgery. As far as I know there is no evidence at present for the existence of "insulinase."

An immunologic cause was first suggested by Lowell[28,29] and Lerman[30] to account for otherwise unexplained resistance to insulin. Local cutaneous allergic reactions to insulin are not uncommon. Rarely, systemic allergic reactions occur. The local reactions seldom interfere with the general effect of insulin. It is not clear whether these reactions are due to insulin or to impurities. Resistance to insulin has been described in association with local or generalized allergy; in most of the reported cases no such association has been observed.

The possibility that resistance to insulin in any given case is due to antibody formation has to be considered. It was for this reason that Arquilla was requested to study the patient's serum. His results offer support for such a basis for insulin resistance in this case.

Summary

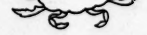
A case of resistance to insulin is reported in a patient whose diabetes mellitus followed total pancreatectomy. This patient is compared with others who survived total pancreatectomy for more than a month.

The demonstration of the presence of antibodies to insulin in this patient's serum is described.

The problem of insulin resistance is briefly reviewed.

References

1. Sunderman, F. W., Austin, J. H., and Williams, P. Studies of serum electrolytes. VIII. Concentration of electrolytes and non-electrolytes in serum following insulin administration in diabetic patients. *J. Clin. Investigation* **11**:1261-1271, 1932.
2. Arquilla, E. R., and Stavitsky, A. B. Immunological detection of microgram quantities of insulin. *Anat. Rec.* **115**:276, 1953.
3. Whipple, A. O. Radical surgery for certain cases of pancreatic fibrosis associated with calcareous deposits. *Ann. Surg.* **124**:991-1008, 1946.
4. Waugh, J. M., et al. Total pancreatectomy: symposium presenting four successful cases and report on metabolic observations. *Proc. Staff Meet., Mayo Clin.* **21**:25-46, 1946.
5. Chapman, H. S. Surgery of pancreas. *West. J. Surg.* **58**:178-187, 1950.
6. Mazingarbe, A., Roussillon, J., Geffroy, Y., and Renault, P. Deux cas de duodénopancréatectomie totale. *Mém. Acad. de chir.* **78**: 771-775, 1952.
7. Gourevitch, A., and Whitfield, A. G. Total pancreatectomy. *Brit. J. Surg.* **40**:104-107, 1952.
8. Cattell, R. B., and Warren, K. W. *Surgery of the Pancreas.* 374 pp. Philadelphia: Saunders, 1953. P. 340.
9. Shay, H., Sun, D. C., and Rosemond, G. Personal communication.
10. Owens, F. M., Jr. Problem of peptic ulcer following pancreatectomy. *Ann. Surg.* **128**:15-20, 1949.
11. Priestley, J. T., Comfort, M. W., and Radcliffe, J., Jr. Total pancreatectomy for hyperinsulinism due to islet-cell adenoma: survival and cure at sixteen months after operation: presentation of metabolic studies. *Ann. Surg.* **119**:211-221, 1944.
12. Fallis, L. S., and Sailagyi, D. E. Observations on some metabolic changes after total pancreatoduodenectomy. *Ann. Surg.* **128**:629-667, 1948.
13. Brunschwig, A., Ricketts, H. T., and Bigelow, R. R. Total pancreatectomy, total gastrectomy, total duodenectomy, splenectomy, left adrenalectomy and omentectomy in diabetic patient: recovery. *Surg., Gynec. & Obst.* **80**:252-256, 1945.
14. Lynch, R. C., and Rosenberg, D. M. L. Intraintestinal hemorrhage following total pancreatectomy for carcinoma of pancreas. *Surgery* **31**:436-442, 1952.
15. Marraffino, B. Total pancreatectomy for adenocarcinoma of pancreas. *New York State J. Med.* **50**:1124-1127, 1950.
16. Warren, K. W. Some aspects of total pancreatectomy. *Lahey Clin. Bull.* **7**:86-96, 1950.
17. Greenfield, J., and Sanders, J. H. Total pancreatectomy with report of postoperative physiologic studies. *Surgery* **25**:824-838, 1949.
18. Dubost, C., Bernier, E., Guéry, J., and Stoïcoïu. Un cas de pancréatectomie totale pour cancer de la tête du pancréas. *Rev. de chir.* **70**:105-117, 1951.
19. Feather, H. E., and Kuhn, C. L. Total pancreatectomy for sarcoma of pancreas. *Ann. Surg.* **134**:904-912, 1951.
20. Nardi, G. L. Metabolic studies following total pancreatectomy for retroperitoneal leiomyosarcoma. *New Eng. J. Med.* **247**:548-550, 1952.
21. Bernard, J., and Touraine, R. Le diabète pancréatoprive de Thomaine. *Gaz. méd. de France* **59**:891, 1952.
22. Sutherland, E. W., and de Duve, C. Origin and distribution of hyperglycemic-glycogenolytic factor of pancreas. *J. Biol. Chem.* **175**: 663-674, 1948.
23. Root, H. F. Insulin resistance and bronze diabetes. *New Eng. J. Med.* **201**:201-206, 1929.
24. Davidson, J. K., and Eddleman, E. E. Insulin resistance: review of literature and report of case associated with carcinoma of pancreas. *Arch. Int. Med.* **86**:727-742, 1950.
25. Smelo, L. S. Lack of response to insulin: report of patient treated with 5,000 units per 24 hours. *South. M. J.* **40**:333-340, 1947.
26. Conn, J. W. Endocrine regulation of blood sugar. *Ann. Int. Med.* **38**:179-187, 1953.
27. Bornstein, J. Insulin reversible inhibition of glucose utilization by serum lipoprotein fractions. *J. Biol. Chem.* **205**:513-519, 1953.
28. Lowell, F. C. Immunologic studies in insulin resistance. I. Report of case exhibiting variations in resistance and allergy to insulin. *J. Clin. Investigation* **23**:225-231, 1944.
29. *Idem.* Immunologic studies in insulin resistance. II. Presence of neutralizing factor in blood exhibiting some characteristics of antibody. *J. Clin. Investigation* **23**:233-240, 1944.
30. Lerman, J. Insulin resistance: role of immunity in its production. *Am. J. M. Sc.* **207**:354-360, 1944.



SPECIAL ARTICLE

THE PHYSICIAN'S RECORDS*

BERTRAM T. UREN

NEW YORK CITY

BECAUSE the medical profession is a combination of professional services and business procedures a certain amount of bookwork is necessary. If it is done in an orderly fashion and not put off it will, within a short time, be accepted as a normal part of the routine that maintains the practice on an efficient level for the benefit of the doctor and the patient as well.

APPOINTMENT BOOK

If patients are to be seen by appointment, this book should be used. Although at the beginning of a practice appointments may be few it is not advisable to use the day book to list appointments. Patients do break appointments and change the hours. Deletions and erasures should not show in the day book.

APPOINTMENT CARDS

These are an important adjunct to the appointment book and can be used freely, unless the appointment is a day or so ahead.

Some cards are printed with a footnote asking the patient to give notification within forty-eight or twenty-four hours if the appointment cannot be kept. Their use is a matter of choice.

Other cards go farther and warn that a regular charge will be made if notification is not received. Their use is not advisable and invariably creates antagonism. Only an older doctor with an outstanding reputation can, if he is so minded, use the cards without regard for what the patient may think.

A broken appointment may be due to circumstances beyond the patient's control, making cancellation impossible. As a good-will builder it is better to write off the appointment time. However, a second broken appointment calls for a warning to the patient not to repeat it.

If a patient, after breaking an appointment, fails to make another one should not write, or send a card, saying that an appointment has been made for such and such a time and asking him to confirm the appointment. Some patients consider this drumming up business.

DAY BOOK

The day book is a record of patients seen each working day, of charges for service and of payments. Since it is also a record for tax purposes entries should be legible and accurate.

It does not have to be a book printed for the purpose. A year book, if the pages for the days are lined, will do. Columns for charges and payments are not necessary.

It should be used in such a manner that its contents are not public property. If a doctor has an assistant the book should be kept in her desk drawer when not in use, necessary entries being made when a patient is not present.

Its use by a doctor who has no assistant is not bound by any set rule except that of keeping the information confidential. Complete entries may have to be made between visits of patients or after office hours.

For a record of patients seen at the office the name of the patient, the charge and then the payment, if any, should be entered, as follows:

NAME	CHARGE	PAYMENT
John Applegate	$5.00	$ 5.00
Harold McNulty	5.00	—
Thomas Prince	8.00	5.00
Mrs. H. B. Larson	5.00	30.00
William Jennings	NC	NC

John Applegate owes nothing. Harold McNulty owes $5. Thomas Prince owes $3. Mrs. H. B. Larson paid $5 for the charge and $25 she owed. William Jennings was not charged.

If the patient is a wife, son, daughter or relative of the head of family his name should be included for an accurate record:

NAME	CHARGE	PAYMENT
Miss Mary Talbot (Arthur Talbot)	$8.00	$8.00

If a wife's given name is preferred for a more personalized form, the name of the head of family should not be omitted:

NAME	CHARGE	PAYMENT
Mrs. Gertrude Nevins (Harry Nevins)	$5.00	$5.00

For a record of patients seen outside the office, and to keep a check on sources of income, one should allow a separation space between the entries for patients seen at the office and those who receive service at a hospital, such as surgery, as well as patients seen at their homes or at a hospital.

Payments received by mail, or from a person who is not a patient for the day, should also be listed separately, as follows:

NAME		PAYMENT
Charles Widmer	Mail	$20.00
T. H. Skolnik	Hand	$25.00

When a charge is to be paid, in whole or in part, by workmen's compensation, hospital plan, another

*Adapted from a chapter entitled "Office Records" in the forthcoming book, *The Physician, His Practice and His Business*, by permission of the publisher, Little, Brown and Company, Boston.

person or some other means, the following entry is recommended:

Name	Charge	Type
Martin Andrews	$15.00	Compensation
Tom Smith	$80.00	Blue Cross $60.00 Patient $20.00
Arthur Goldsmith	$65.00	Carry Corp. 1256 Drew Lane City

Circling the charge is a warning not to bill incorrectly.

Patient's Record

This consists of a record of the service, the date and the name of the person to whom given. It is written or typed on a file card (4 by 6 or 5 by 8 inches), or letter-size paper, and subsequently filed.

Care should be exercised that the record is complete and that no note of minor service given to a new patient is omitted, in the belief that he will not return for further service. Such a statement may become part of a legal action or may be required for future reference.

For a family record, the head of the family should be indicated as the patient. When a member of the family receives service his name immediately follows the date and the preceding description of service.

When the card system is used the record can be on a separate card or combined with the account record. This combination card allows space for recording charges, payments and balance due.

Some physicians prefer the combination card, which eliminates the necessity of preparing and filing two cards. Others prefer the two-card system, since it separates the service from the charge. Also, when used in front of a patient who owes a bill, it does not serve as a reminder that the doctor while recording the service is also thinking that he should record payment instead of waiting to receive it from billing.

The combination card, in the event of a legal action, would show payments for services, which is a confidential matter between doctor and patient. As a practice grows, cards to be filed may be left on the doctor's or the assistant's desk, where patients will see them. Although the description of service may be unreadable the patient's name and pattern of payment can be taken in at a glance—a possible forerunner for gossip detrimental to a practice located in a neighborhood.

Before either type of card is selected it may be wise to consult an older physician for the benefit of his long experience. Cards printed especially for general practice and some of the specialties are frequently inadequate.

Many doctors complain that the fronts of these cards are wasted when not applicable to a patient's service requirements, or insufficient when applicable, particularly for positive findings. And some specialists complain that they are not up to date for the recording of positive and negative findings.

Consequently, these physicians use their own cards, chiefly 5 by 8 inches and lined front and back. The only printing is a heading on the front that includes name, address, telephone number, referring physician and remarks. Some doctors have nothing printed. Some specialists have "positive" and "negative" printed, according to personal preference.

Account Record

This may be a report of the patient's name, date of service, charge, payment and balance due entered on a file card and subsequently filed or on a loose-leaf sheet, filed in a ledger. It is also a reference for billing.

It can be combined with the patient's record, and the entries made after the complete notation of service on a card 4 by 6 or 5 by 8 inches, printed on both sides. Or it can be a separate card—the letter-size patient's record always requires the separate card.

The space for service is for the name of the patient when he is not the head of the family, and for abbreviations, such as OV (office visit), OV inj. (office visit in addition to injection) and surgery. This facilitates itemizing of first bills.

Data for this card (the patient's name, charge and payment) can be taken from the day book, and the address of a new patient from the patient's record. Service may be indicated by the charge; otherwise, it can be taken from the patient's record.

A card that does not have a column for balance due should not be used. Its omission means extra billing effort in time taken to total the amount due. Also, it is essential that the balance be kept up to date, showing exactly what is due:

Date	Description of Service	Charge	Payment	Balance Due
Enter	Enter	$15.00	- - -	$15.00
Enter	None	- - -	10.00	5.00
Enter	Enter	10.00	15.00	- - -
Enter	Enter	25.00	10.00	15.00

Broken lines (- - - - -) always indicate no charge when there was no service, or nothing paid at the time of service, or no balance after payment.

Workmen's compensation or medical-plan payments in full are recorded as follows:

Date	Description of Service	Charge	Payment	Balance Due
Enter	Enter	$125.00		Compensation
		or		
Enter	Enter	125.00		Blue Cross

When the medical plan pays only part the patient is billed for the full amount, if payment is not made before the first of the month:

Date	Description of Service	Charge	Payment	Balance Due
Enter	Enter			
	(Blue Cross 80.00)	125.00	- - -	125.00
Enter	None Paid by Blue Cross	- - -	80.00	45.00
Enter	None Paid by patient	- - -	45.00	- - -

When payment is to be made by another person and the patient owes a balance after that charge is paid the record is as follows:

Date	Description of Service	Charge	Payment	Balance Due
Enter	Enter	$50.00		J. Henry & Sons
				42 Warren Street
				City
Enter	Enter	15.00	- - -	15.00
Enter	None Paid by J. Henry	- - -	50.00	15.00

One must be careful not to omit a card for a patient who pays, no matter how small the amount. A charge entered in the day book must show on an account record.

If an adequate card cannot be found a printer will order cards lined on both sides, and print accordingly.

Filing

Case number is not necessary and would require a double filing system. When a patient's name is typed for filing the more practical system is the first name first (Henry Adam) rather than the last name first (Adam, Henry).

Patient's Record

The letter-size record requires an individual folder for each patient and is filed under "patients." Some doctors file a new patient's record under "miscellaneous" and use the individual folder only when the patient returns for further service.

A card record that is not combined with the account record is filed under "patients." The combined record is filed under one of two groups, "paid accounts" and "unpaid accounts," to facilitate billing.

Account Record

This is filed under one of two groups, "paid accounts" and "unpaid accounts."

Loose-leaf sheets should also be filed in the ledger under one of the two groups.

Reports of Workmen's-Compensation and Medical-Plan-Clinic Payments

These can be filed in individual folders marked with the patient's name, or in a special folder marked "compensation" and so forth. When a special folder is used one should file alphabetically, not merely open the folder and insert the report haphazardly.

Discussion of Bills with Patients

A patient seen for the first time may cause the physician some difficulty in knowing what to say, or do, about the charge.

When a patient asks if he should pay at the time of a visit or if he is to receive a bill the doctor's best answer, with friendly emphasis on the first three words, is, "Well, you can save me or my assistant the trouble of acting the part of a bookkeeper. I can bill you, if you prefer."

When a patient says, "Please send me a bill," the only reply should be co-operative agreement. When nothing is said it fosters good will to say nothing, in turn, and bill for the first of the month. This also applies to house calls.

The charge may invite discussion, particularly when it is fairly large, payment in a lump sum seems questionable and the doctor is agreeable to partial payments within a reasonable time.

Discussion is far removed from commercialism when it is a sincere effort to help the patient meet his obligation, by means of some arrangement for payment that is satisfactory from the standpoint of his finances.

After an arrangement has been made the patient should not be asked to sign an agreement. If inviting the discussion proves an error and the patient is shown up as one who habitually fails to meet his obligations he will represent the minority. For it is an established fact that most patients who owe medical bills are honest.

Billing

Patients are billed according to the balance shown on the account record, the separate card or the card combined with the patient's record. A set rule for billing is to mail bills to reach patients on the first of the month, and every necessary month, thereafter.

Some doctors postpone until the next month charges incurred toward the end of the month—the 25th, or 26th or 27th. This allows several days to prepare bills. Also, it is good psychology not to bill for services rendered practically the day before.

To ascertain whether the rule of first-of-the-month billing is rigidly applied each month one leaves a space at the bottom and across the front and back of the account record for entering the date bills are sent. Space on the combination card is a matter of choice.

Ignoring the billing rule is the reason why some doctors are the last to be paid, if they are paid at all. Billing on different days each month or omitting bills for one month or more is a haphazard procedure that invites patients to delay paying by creating the impression that the doctor can afford to wait.

Furthermore, bills should be addressed to the person legally responsible for payment, showing the patient's given name and not Mr., Mrs. or Miss Doe, which is lacking in courtesy. The bill for extra charges, consultation and so forth should be fully explained to the patient, to avoid possible controversy.

Also, the first bill should be itemized. This gives the patient a check on services and charges. Billing for "services rendered" when there were many charges does not present a true picture; the patient sees only the total. The extra effort will pay extra dividends.

Itemized billing for several identical charges is made as follows:

House Calls (12) January 2, 3, 4, 6, 8, 10, 10, 11, 12, 13, 14, 15	$84.00

Itemized bills for average charges contain the following information:

January 18	OV	$5.00
January 19	HC	7.00
January 21	OV X-ray	20.00
		$32.00

Itemized billing for the head of the family list the members of the family; no listing indicates that he received the service:

January 4	Mary OV	$5.00
January 5	Mrs. Talbot HC	7.00
January 10	OV inj.	8.00
		$20.00

Billing for charges that were itemized in the last bill show as "previously rendered," new charges during the month also being itemized as follows:

Previously rendered		$46.00
January 8, 8, 10	HC	21.00
		$67.00

If part of the itemized bill was paid during the month, it is shown as "balance due" and not as "previously rendered."

Billing for a charge that includes postoperative care always shows the weeks or months:

January 18	Surgery	$250.00 including three months' postoperative care.

Billing for compensation shows the patient's case number and the name of his employer. Items are given in full, with no abbreviations. A duplicate is kept in the file; such bills have been known to go astray. Subsequent monthly bills are not necessary. If payment is not made within a reasonable time, an inquiry should be made. If, after the first bill, additional service is given, the bill is for that charge, or charges; it does not refer to the previous bill rendered. Care should be exercised that authorization is received from the insurance carrier to render further service, that the charge conforms to the schedule of allowances and that reports — particularly "progress reports" — are made as required. When one is in doubt regarding procedure the carrier will prove helpful.

Before billing for an accident case one should have a thorough understanding with the patient about the bill. If it is to be legal and payment made when the case is settled, the patient should arrange with his lawyer to protect the doctor's interests.

Failure of Billing

A medical bill, unlike a commercial bill, is usually incurred with no agreement about payment. Consequently, it is a reminder of the debt, not a request for payment.

Therefore, payment from billing alone may be entirely dependent on what the patient considers a reasonable time or may be based solely on his experience with the billing systems of other doctors. He may simply wait until payment is requested or, in the minority of cases, until it is demanded.

Too many human factors prevent setting a limit on the number of bills, except that, on the average, a minimum of three bills should be sent before one decides whether to continue bills or to request payment.

The first step in making the request is a footnote on one, two or three bills. Footnotes can be repeated: *"Please accept this as a reminder that payment will be appreciated"* or *"If there is any reason why payment cannot be made, please communicate with me."* When there is no response to the first step the physician does not return to bills as usual. Wide experience has shown the need for a second step, either a telephone call by the assistant ("Is there any reason for your failure to reply to the footnoted bills?") or an amicable letter, not a collection letter demanding payment:

> My office has brought to my attention your failure to reply to the footnoted bills, regarding your account of $50.00.
> As I am most eager to co-operate with you, I shall appreciate your communicating with me within the next few days.
> Thank you.

If no response is received a second amicable letter, sent two weeks later in a plain envelope, often proves effective in place of the collection letter:

> I am wondering whether your failure to reply to my letter of [date] is an oversight, or whether there is any particular reason why payment should not be made at this time.
> If you will let me hear from you I am confident that we can arrange liquidation to our mutual satisfaction.

Lack of response indicates that the collection letter, sent in a plain envelope, can now be used without loss of good will:

> I regret that I have to advise you that (if your account of $50.00 is not paid in full) (if a satisfactory arrangement for payment of your account of $50.00 is not made) within seven days from today's date, I shall place it in the hands of my (attorney) (collector).
> I hope you will make this action on my part unnecessary.

If there is no response ten days later the bill is placed for collection. The action will be justified.

Collection Agencies

It is best not to choose a collection agency that retains the right to keep an account as long as it pleases. Another agency may be able to collect. Difficult accounts require persistent effort, which is not made if, after writing a few letters, the first agency merely files the bill.

Long years of personal experience covering many thousands of patients who owed medical bills has shown unequivocally that placing an account for collection, after amicable procedure has failed, creates no ill will for the doctor, even when his office is in a residential area and even if he unwittingly engages an agency that is unduly severe.

The only time when the action causes loss of good will is when the physician violates a fundamental collection principle by demanding payment instead of first requesting it. Antagonism is created, for the patient believes that he was not given the chance to pay in a decent manner and that he was not met halfway.

MEDICAL PROGRESS

INTERMEDIARY METABOLISM*

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BOSTON

IN the past decade biochemists have turned more and more from analyses of the static condition of tissues to a consideration of the dynamics of tissue metabolism. This has been made possible by the availability of isotopes, both heavy and radioactive, and by the development of accurate and reliable methods of working with them. Biochemists have had to adapt the standard methods of organic syntheses to a microscale and to devise new methods for the synthesis of compounds labeled in a particular atom of the molecule. Still other methods have been discovered for the degradation of the products of metabolism by means of which the amount of label in each atom of the molecule—for example, in each of the six carbons of a glucose molecule—could be determined.

The use of heavy or radioactive isotopes involves the assumption that the enzymes of the body do not differentiate a labeled and an unlabeled atom but handle the two in the same way and at the same rate. For the very low concentrations of labeled atoms ordinarily used in tracer studies there is ample evidence that this is true. However, at high concentrations of a labeled atom, the difference in mass between the two types of atom may influence the rate of reaction. A number of C^{14}-labeled substances were found to react at rates as much as 15 per cent less than those for the analogous unlabeled substances.[1] The greatest percentage difference in mass is found between hydrogen and deuterium, and it is not surprising that high concentrations of heavy water are poisonous. Thorn[2] prepared succinic acid labeled with deuterium in the methylene groups at a level of 77 atoms per cent—that is, 77 out of every 100 hydrogen atoms had been replaced by deuterium. It was found that this was oxidized by heart-muscle succinic oxidase at a rate only 40 per cent as great as that of normal succinate.

Studies with labeled substrates have provided a great increase in understanding of intermediary metabolism, which has brought to light some unexpected facts, facts such as the prominent role of one-carbon and two-carbon compounds in metabolism and the ready interconversion of carbohydrates, fats, proteins, steroids, porphyrins, purines and pyrimidines. In recent years the role of vitamins in the body has been even better understood. In each case in which a definite function can be assigned to a particular vitamin it has been found to serve as an important part of one or more coenzymes. Yet, although it is known, for example, that thiamine, as thiamine pyrophosphate, is necessary for the metabolism of pyruvic acid and it is clear that a deficiency of thiamine results in some interference in the metabolism of this key three-carbon intermediate, it cannot be stated just how this metabolic lesion leads to the signs and symptoms of vitamin deficiency.

There have been many efforts to elucidate the role of hormones in regulating metabolism, and although a number of metabolic functions have been shown to be influenced by hormones both in vivo and in vitro, no hormone has been shown conclusively to control a particular metabolic reaction.

Some of the greatest recent advances in biochemistry have dealt with the release of energy from substrate molecules in a form available for utilization in biological work. The discovery of high-energy phosphate bonds over a decade ago was followed by revelations of how these bonds are generated, first in glycolysis and later in the Krebs tricarboxylic (citric) acid cycle. Biochemists are currently engaged in studies of what is now known to be the most important source, quantitatively, of high-energy phosphate bonds, the phosphorylations that occur, in some manner as yet unknown, during the transfer of electrons from substrate to oxygen. The discovery of coenzyme A led to the realization that there are energy-rich thioesters that are just as important in metabolism as energy-rich phosphate esters and, indeed, that the energy of one type of bond can be transferred to another.

The development of practical high-speed centrifuges has made possible the separation of cell particles—nuclei, mitochondria and microsomes—and the realization that cells have a chemical architecture. Certain enzymes are found in certain parts of the cell and not in others—the mitochondria, for example, have proved to be sacks of oxidative enzymes, the microsomes to be exceptionally rich in protein-synthesizing enzymes and so on.

The shift in interest to studies of intermediary metabolism has not obviated the need for careful analytical chemistry; indeed, it has increased it. The

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development of methods for separating closely similar compounds by countercurrent distribution and by chromatography on filter paper, ion-exchange resins or silica-gel columns has made possible the separation and identification of small amounts of a wide variety of compounds. By the use of suitable eluting solutions one can separate amino acids, sugars, phosphorylated intermediates, Krebs-cycle acids, steroids, nucleotides and so on. These can then be demonstrated qualitatively by color reactions on the paper, or the separated substances may be eluted and quantitative estimates

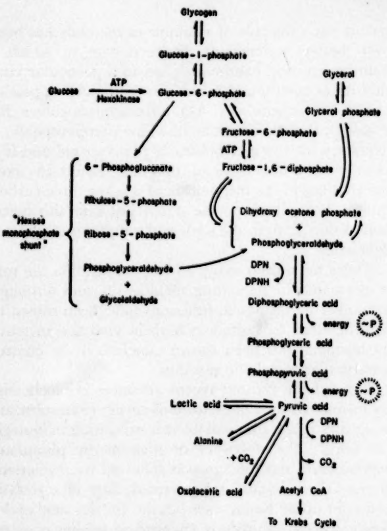

FIGURE 1. *Pathways of Glycolysis by Which Glucose and Glycogen Are Metabolized to Pyruvic Acid.*

Some of the many possible fates of pyruvic acid are indicated: its reduction to lactic acid; its conversion by transamination to alanine; the process of carbon dioxide fixation by which oxalacetic acid (oxalacetate) is formed; and its conversion to acetyl coenzyme A. The hexose monophosphate shunt is an alternate path from glucose-6-phosphate to phosphoglyceraldehyde.

of the amounts present made by the use of standard chemical methods.

In the following discussion it is necessary to consider separately the intermediary metabolism of each of the major types of biochemical compounds. It must be kept in mind, however, that tracer studies have provided ample evidence that all these pathways are intimately interrelated and that the divisions between them are artificial.

CARBOHYDRATES

The glycolytic pathway by which glucose or glycogen is converted, through a series of phosphorylated intermediates, to pyruvate has been repeatedly confirmed and found to occur in a wide variety of tissues (Fig. 1). Racker and Krimsky[3] have shown that the conversion of phosphoglyceraldehyde to 1,3 diphosphoglyceric acid involves a sulfhydryl group of the enzyme, presumably the —SH group of a tightly bound glutathione molecule. Racker postulates that DPN (diphosphopyridine nucleotide) is bound to this —SH group. The first step in enzyme action occurs with the cleavage of the sulfur-DPN bond by the aldehyde group of the substrate to yield reduced DPN (DPNH) and the substrate bound to the enzyme as a thioester. The thioester is then split by phosphorolysis with inorganic phosphate to give the free enzyme-SH group and diphosphoglyceric acid, with an energy-rich phosphate bond.

An alternative pathway, sometimes referred to as the "hexose monophosphate shunt," has been shown to occur in yeast, certain bacteria and mammalian tissue (Fig. 1). In this reaction glucose-6-phosphate is oxidized to 6-phosphogluconate[4] (TPN, or triphosphopyridine nucleotide, is the hydrogen acceptor); this, in turn, is oxidized to the ketopentose, ribulose-5-phosphate (TPN, again, is the hydrogen acceptor), which is converted to ribose-5-phosphate.[5] This is probably the source of the ribose used in the synthesis of nucleotides and nucleic acids. The pentose phosphates are apparently split to triose phosphate and a two-carbon compound, which may be glycolaldehyde. The triose phosphate enters the usual glycolytic system; the fate of the two-carbon compound is unknown—it may combine with another mol of pentose phosphate to form a phosphorylated seven-carbon sugar. Similar seven-carbon phosphates accumulate very early in photosynthesis by green plants.[6] Bloom et al.[7] have shown that this hexose monophosphate shunt is quantitatively important in mammalian liver, accounting for 75 per cent of the glucose-6-phosphate metabolized. It is much less active in heart, brain and skeletal muscle.[5] Racker[8] has demonstrated the synthesis of desoxyribose-5-phosphate from acetaldehyde and glyceraldehyde-3-phosphate, a reaction catalyzed by desoxyribose phosphate aldolase.

The importance of the intracellular ionic environment in controlling intermediary metabolism has been strikingly demonstrated by Hastings and his collaborators.[9] Rat liver slices are unable to synthesize glycogen when incubated in a medium low in potassium. Conditions that maintain the intracellular potassium concentration at its normal value favor the formation of glycogen from both glucose and pyruvate. Lowered potassium concentrations decrease glucose uptake by the liver slice but enhance the conversion of pyruvate to glucose. The ionic environment was one factor determining whether or not hormone effects could be demonstrated in vitro. The experiments are important in showing that potassium has important functions besides simply maintaining the intracellular fluid mass.

Since the postulation of the Krebs tricarboxylic acid cycle[10] research has shown that it occurs almost universally in animal and plant tissues and that it is the final common pathway for the metabolism of amino acids and fatty acids as well as for the pyruvic acid derived from glycolysis (Fig. 2). At one time data from C^{14} experiments apparently ruled out citric acid as a member of the cycle, for the distribution of radioactivity was such that no symmetrical tricarboxylic acid could be part of the cycle. However, Ogston[11] pointed out that, if the enzyme made a three-point attachment with its substrate, the attachment could occur in only one way and the substrate would be handled as though it were asymmetrical. Subsequent experiments[12] revealed that citric acid is the first product of the condensation of oxalacetic acid and acetyl coenzyme A (CoA).

The identification of "active acetate" as acetyl CoA[13,14] showed the metabolic function of the vitamin, pantothenic acid, solved the mystery of the exact nature of active acetate and demonstrated the existence of a second type of energy-rich bond—the energy-rich thiol ester. It has since been found that CoA is involved in the transfer of many different types of acyl groups: acetoacetate, succinate and fatty acids. The molecular structure of CoA has been determined,[15] and, like DPN, TPN and FAD (flavin adenine dinucleotide), it was found to contain adenosine pyrophosphate (ADP). In coenzyme A the ADP is joined to pantothenic acid, which in turn is bound by a peptide bond to beta-mercaptoethylamine. Analyses show that most, if not all, of the pantothenate present in tissues is there as CoA; this is the only known form of pantothenic acid that is active biochemically.

Another coenzyme, called lipoic acid or thioctic acid, has been found to be important in the oxidative decarboxylation of pyruvic acid and in the generation of acetyl coenzyme A.[16] Reactions that decarboxylate pyruvate to acetaldehyde or acetoin, ones in which there is no oxidation, require only thiamine pyrophosphate as the coenzyme. Oxidative decarboxylations of pyruvate, which yield "active acetate," require lipoic acid in addition.[17]

Lipoic acid is 6,8-dithiooctanoic acid, an eight-carbon, straight-chain fatty acid with a five-membered disulfide ring at the end away from the carboxyl group.[18] It is active in extremely small amounts, resembling vitamin B_{12} in this respect. Although some, at least, of its functions in intermediary metabolism are known, it has not yet been shown to be a necessary component of the diet of higher animals, and all attempts to cause a lipoic acid deficiency in animals have been unsuccessful. Reed and DeBusk[19] produced by irradiation a strain of *Escherichia coli* that was unable to grow on a basal medium enriched with lipoic acid but could grow on one enriched with an unknown, combined form of lipoic acid. They were able to characterize this combined form as lipoic acid bound by an amide linkage to thiamine pyrophosphate. They then synthesized lipothiamide, which was active in their test organism. Additional evidence from experiments with cell-free extracts of these *Esch. coli* mutants led them to the conclusion that lipothiamide pyrophosphate (LTPP) is the actual coenzyme for the oxidative decarboxylation of alpha-keto acids such as pyruvate and alpha-ketoglutarate.

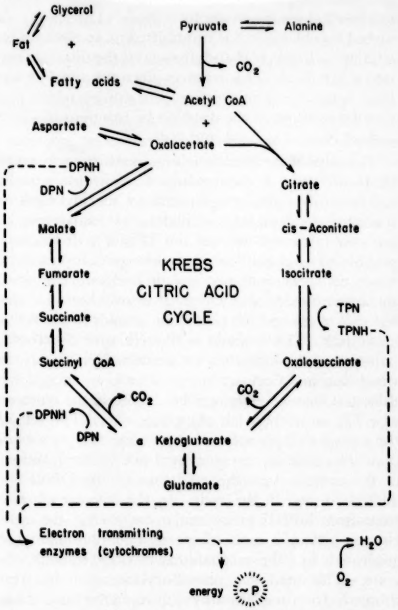

FIGURE 2. *The Krebs Citric (Tricarboxylic) Acid Cycle. Acetyl coenzyme A, formed from pyruvate or in the oxidation of fatty acids, condenses with oxalacetate to form citrate. The path of the protons and electrons removed in the cycle as DPNH or TPNH is indicated.*

Reed and DeBusk[20] formulate the role of LTPP in pyruvate oxidation as follows:

$$CH_3C^{*O}COO^- + \begin{matrix}S\\|\\S\end{matrix}\rangle LTPP \rightleftarrows CH_3-C^{*O}-\begin{matrix}S\\|\\S\end{matrix}\rangle LTPP + CO_2 \quad (1)$$

$$CH_3C^{*O}-\begin{matrix}S\\|\\S\end{matrix}\rangle LTPP + CoA-SH \rightleftarrows \begin{matrix}HS\\|\\S\end{matrix}\rangle LTPP + CoA-S-C^{*O}-CH_3 \quad (2)$$

$$\begin{matrix}HS\\|\\S\end{matrix}\rangle LTPP + DPN^+ \rightleftarrows \begin{matrix}S\\|\\S\end{matrix}\rangle LTPP + DPNH \quad (3)$$

Acetyl LTPP was isolated from the reaction mixture, and analysis supported the proposed structure. Since it can transfer its acetyl group reversibly to CoA acetyl LTPP is presumably an energy-rich thioester and may be an additional kind of "active acetate." LTPP is unique in that this one coenzyme serves as both an electron and an acetyl acceptor from pyruvate (reaction 1). Other experiments suggest that the acetyl group must be transferred to acetyl CoA before

it can be used for the synthesis of citrate, acetoacetate or acetyl sulfanilamide. Further investigations show that a sequence of reactions comparable to 1-3 above will oxidatively decarboxylate alpha-ketoglutaric acid and produce succinyl CoA, with succinyl LTPP as the intermediate compound.

Calvin and Barltrop[21] have suggested that lipoic acid may be involved in the conversion of light energy to chemical energy in photosynthesis. The energy absorbed by chlorophyll is transmitted as an electron excitation to lipoic acid and dissociates the disulfide ring into a biradical. This removes electrons and H^+ ions from a suitable donor to form the dithiol, which may then be oxidized to the disulfide by reactions in which carbon dioxide is fixed and reduced.

The steps of the Krebs cycle — oxalacetate + acetyl CoA → citrate → cisaconitate → isocitrate → oxalosuccinate → alpha-ketoglutarate → succinyl CoA → succinate → fumarate → malate → oxalacetate — are now fairly well worked out (Fig. 2). It has been possible to estimate how many energy-rich phosphate bonds are generated per mol of pyruvate converted to carbon dioxide and water. It seems clear that only one mol of energy-rich phosphate is made in the Krebs cycle itself. This is made in the oxidative decarboxylation of alpha-ketoglutarate described previously, in which succinyl CoA is formed. This is an energy-rich thioester, whose energy may be utilized in the synthesis of ATP, an energy-rich phosphate ester. The rest of the energy-rich phosphate bonds, about 14 per mol of pyruvate oxidized, are generated not by the reactions in the cycle but in the oxidation of the DPNH or TPNH formed in the cycle. In the transfer of electrons from DPNH to molecular oxygen via the cytochrome system 3 mols of energy-rich phosphate are generated, but the mechanisms involved remain obscure. This oxidative phosphorylation can be "uncoupled" from oxidation by dinitrophenol and, it has been reported,[22] by thyroxine. Weil-Malherbe[23] has suggested that the greater than normal respiration of dystrophic muscle from animals deficient in vitamin E may be due to a selective inhibition of the energy-coupling mechanism.

It is believed that in the process of electron transfer labile phosphorylated intermediates are formed that transfer the phosphate and its associated energy to ADP to form ATP (adenosine triphosphate), and that dinitrophenol uncouples this by splitting the intermediates before they can transfer the phosphate. This area of intermediary metabolism is now being investigated in a number of laboratories.

There are four reactions in the Krebs cycle in which DPNH or TPNH is generated, and the oxidation of these yields 3 mols of high-energy phosphate per mol of DPNH for a total of 12 mols of energy-rich phosphate. In the oxidation of succinate to fumarate, the hydrogens removed are not transferred to DPN; instead, their electrons are transferred to cytochrome B and the transfer of these electrons through the cytochrome system to molecular oxygen yields 2 mols of energy-rich phosphate.[24] These 2, as well as the 1 of energy-rich phosphate made at succinyl CoA and the 12 made in the oxidation of DPNH, total 15 per mol of pyruvate. Since the over-all oxidation of pyruvate requires 5 atoms of oxygen, this gives an average P:O ratio (mols of energy-rich phosphate made per atom O used) of 15:5 or 3.

Since each mol of glucose yields 2 mols of pyruvate the oxidation of the 2 mols of pyruvate derived from 1 mol of glucose would yield 2 by 15 or 30 mols of energy-rich phosphate. In addition the metabolism of glyceraldehyde phosphate to pyruvate yields 5 mols of energy-rich phosphate per mol—1 at diphosphoglyceric acid, 1 at phosphopyruvic acid and 3 from the DPNH generated in the phosphoglyceraldehyde dehydrogenase step. The 5 mols of energy-rich phosphate generated per mol of triose would total 10 mols per hexose metabolized to pyruvate, or a total of 40 mols per mol of glucose metabolized completely to carbon dioxide and water. Since 2 mols of energy-rich phosphate are required to metabolize glucose to the fructose diphosphate stage, which splits to yield 2 mols of triose phosphate, there is a net synthesis of 40 − 2, or 38 energy-rich phosphates per mol of glucose. If it is assumed that each energy-rich phosphate bond equals 12 kilocalories this represents an efficiency of about 68 per cent in the conversion of the energy of a glucose molecule to biologically available energy.

As more of the details of intermediary metabolism have become known it has become clear how glycolysis and cell respiration may be regulated to fit the moment-to-moment requirements of the cell.[25] The lowest rate of oxygen consumption by a cell in vivo is presumably determined by the energy requirements of that cell for its basal metabolic functions and the maintenance of its cellular structure. When the cell is stimulated to do work—to secrete something, to contract, to conduct, or to synthesize some organic molecule—ATP breaks down to supply the energy, and in the process inorganic phosphate is released. The equilibrium between glycogen + inorganic phosphate ⇌ glucose-1-phosphate is shifted to the right, and more glucose-1-phosphate is made available. The increase in this substrate speeds glycolysis and increases the production of pyruvate. The oxidation of pyruvate by the citric acid cycle and the associated oxidative phosphorylation by the respiratory-chain enzymes requires inorganic phosphate and phosphate acceptors, which are made available by glycolysis. These oxidative reactions resynthesize high-energy phosphate from inorganic phosphate. After the work has been performed and the stimulus has been withdrawn respiration will continue at an accelerated pace only until the concentrations of inorganic phosphate and phosphate acceptors are reduced and the cell restored to its original state. McIlwain[26] presented experimental evidence that this sequence occurs in brain slices stimulated electrically in vitro: creatine phosphate

decreases, inorganic phosphate increases, and both glycolysis and respiration increase.

Proteins

One of the most spectacular accomplishments of biochemists in recent years has been the determination, by Sanger and Tuppy[27] and Sanger and Thompson,[28] of the number and order of the amino acids that comprise the insulin molecule. These analyses show that each insulin molecule (molecular weight about 12,000) consists of 4 peptide chains, 2 of one type (A) and 2 of another (B), crosslinked by the disulfide bonds of cystine. By a combination of chemical and enzymatic hydrolyses the authors split each chain into a number of different dipeptides, tripeptides and tetrapeptides, isolated each by ion-exchange resins and paper chromatography, labeled the N-terminal amino acid with dinitrofluorobenzene and then hydrolyzed the peptides and identified their constituent amino acids. The final piecing together of the evidence concerning the order of all the constituent amino acids was a brilliant piece of deduction. The A polypeptide chain contains 21 amino acids and has glycine as its N-terminal amino acid. Phenylalanine is the N-terminal amino acid of chain B, which is composed of 30 amino acids. Slight differences have been detected between insulins from different animal species. Other proteins and peptides analyzed by analogous methods are ACTH, oxytocin, lysozyme and ribonuclease. Oxytocin was found to be a peptide containing 8 amino acids; it has been synthesized by du Vigneaud and his colleagues [29]

The classic work of Schoenheimer[30] and his colleagues demonstrated that the tissue proteins are not stable, inert structural substances but labile ones that are constantly being broken down and resynthesized. Schoenheimer's studies were made with amino acids labeled with heavy nitrogen, N^{15}; most of the more recent studies have used C^{14}-labeled amino acids. It has been postulated that the lability of the structural proteins enables cells to adapt to varying conditions by growth, by producing enzymes or antibodies, or in other ways. Many experiments have given evidence that proteins become radioactive after incubation with a radioactive amino acid. The assumption that this indicates the incorporation of the amino acid into the protein by true peptide bonds has been proved rigorously, in at least 1 experiment,[31] by the isolation of radioactive aspartic acid from a hexapeptide obtained by partial enzymatic hydrolysis of egg albumin. The egg albumin was produced in vitro by incubation of minced hen's oviduct in a C^{14} bicarbonate medium. From a variety of experiments carried out both in vivo and in vitro it is apparent that rat-liver proteins have a half-life of about seven days—that is, half the amino acids in liver proteins are replaced every week. The average half-life of the total protein in man is estimated to be eighty days, with a more rapid turnover in liver and a slower replacement rate in muscle proteins.[32]

More recently, interest has centered on the mechanisms of protein synthesis and the question whether protein molecules are built directly from amino acids or from intermediate peptides. Although protein synthesis, as measured by the rate of incorporation of labeled amino acids, takes place in all parts of the cell, it occurs most rapidly in the microsomes.[33,34] Fetal tissues incorporate amino acids into proteins faster than adult tissues, and tumor tissues are usually found to incorporate amino acids into proteins faster than the corresponding normal tissues. Usually, when tissues are incubated in vitro with labeled amino acids, there is a net decrease in the total protein of the tissue even though the amino acid is incorporated at a rate comparable to that of the tissue in vivo. In 1 case, however, a net synthesis of protein in vitro has been demonstrated—the synthesis of serum albumin by chicken-liver slices.[35] It has been widely postulated that ribonucleic acid plays an important part in protein synthesis.[36] This postulation is based on several types of indirect evidence, but so far no direct evidence has been obtained. There is no clear-cut evidence on the mechanism of protein synthesis or on the part, if any, that ribonucleic acid might play.

The incorporation of a labeled amino acid into a protein might entail the complete breakdown of the protein molecule and its resynthesis from amino acids, or simply the opening and reclosing of a few peptide bonds to allow the exchange of an unlabeled for a labeled amino acid. Experiments suggesting the former mechanism are those of Geiger,[37] who fed animals a diet lacking an indispensable amino acid and then fed this amino acid separately. If the animal received this single amino acid more than a few hours after the mixture of all others, growth did not occur, although it did take place if exactly the same amount of the amino acid was given to the animal at the same time as the main amino acid mixture. This suggests that protein synthesis can occur only if all necessary amino acids are present at concentrations greater than the fasting level.

Since it appears unlikely from a consideration of the energy relations involved that protein synthesis could occur by a simple reversal of hydrolysis, a search has been made for some energy-rich amino acid intermediate that could provide the energy for peptide-bond synthesis. Phosphorylated amino acids and dehydropeptides have been considered and discarded as possible intermediates.[38,39] The fact that rats deficient in pantothenic acid have a severely decreased ability to produce antibodies suggests that CoA is necessary for the synthesis of proteins, possibly in the production of acetylated amino acids, which may be intermediates in the process.[40] The ability of the rats to synthesize antibodies is restored by feeding of pantothenic acid. The CoA-catalyzed acetylation of amino acids has been demonstrated in extracts of bacterial

cells, but the relation between CoA and peptide synthesis remains to be elucidated.[41]

The experiments on the synthesis of egg albumin in vitro by the hen's oviduct suggested that the protein was not synthesized simply from a single pool of amino acids, for when the molecule was split enzymatically, aspartic acid or alanine isolated from the two parts had quite different amounts of radioactivity.[31] The amino acids isolated from the hexapeptide portion were more radioactive than those from the residue. Anfinsen and Steinberg[31] postulated the existence of peptides as intermediates in protein synthesis to explain this differential labeling. Muir, Neuberger and Perrone,[42] in contrast, found no difference between the radioactivities of the terminal versus the nonterminal valines isolated from hemoglobin synthesized by the rat injected with labeled valine.

The phenomenon of transamination, by which an amino group is transferred from an amino acid to a keto acid, was described in 1937 by Braunstein and Kritsman.[43] Although transamination was originally considered to be a limited reaction more recent studies have shown it to occur in a wide variety of tissues and with practically all amino acids as long as glutamate is one of the pairs. A number of different keto acids can serve as the amino group acceptor. Pyridoxine (vitamin B_6), as pyridoxal phosphate, is the coenzyme needed for all transaminase reactions. The actual mechanism of amino group transfer and the intermediates involved are not yet clear. By transamination the carbon chains of alanine, glutamate and aspartate may be converted to pyruvate, alpha-ketoglutarate and oxalacetate, respectively, and thus serve as links between the intermediary metabolism of proteins and carbohydrates (Fig. 1). By the reverse of these reactions, labeled carbon introduced into the system as glucose or carbon dioxide can rapidly be incorporated into proteins.

The discovery of these transaminases and of other reactions that transform one amino acid into another explains why certain amino acids are "essential"—why they must be present in the diet—and others are not. Alanine, glutamate and aspartate can be made by transamination and hence need not be ingested as such. A number of others can be made from these. The "essential amino acids" are simply those that cannot be made, or made in sufficient amounts, by the cells of the body and hence must be present in the diet.

Pyridoxal phosphate serves as the coenzyme for a great variety of enzymes catalyzing reactions of amino acids other than transamination,—for example, decarboxylation, dehydration, deamination and desulfhydration.[44] The number and variety of the reactions requiring pyridoxal phosphate are so great that it can be considered as necessary for practically all enzyme-catalyzed reactions involving the degradation, interconversion and synthesis of amino acids.

Experiments with labeled amino acids have shown how the tissues of the body put together complex molecules from simpler ones. The amino acid glycine has been shown to be the source of much of the heme molecule, the functional part of hemoglobin, the cytochromes and certain other biologically important substances.[45] Glycine also forms an integral part of creatine,[46] important in muscle contraction as phosphocreatine, and of the purine ring structure, found in adenine or guanine in nucleic acids and free nucleotides such as ATP and DPN.[47]

In a series of interesting papers Christensen and Henderson[48] have shown that cells have the ability to concentrate amino acids within their cytoplasm and thus, presumably by an energy-requiring, enzymatic reaction, to "pump" amino acids from the extracellular to the intracellular phase. These reactions are involved in the transfer of amino acids from one extracellular phase to another, in the absorption of amino acids from the gut, their reabsorption from the kidney tubules to the blood stream, and their transfer from maternal to fetal blood across the placenta. Every cell must have a sufficient supply of each of the 25 or more amino acids to provide for protein synthesis, and the importance of this concentrating mechanism is clear. Since a high level of one amino acid can prevent the cell from taking up other amino acids, there is probably only one mechanism for the transport of amino acids across the cell membrane, and the various amino acids compete with each other for places on the carrier mechanism.

Fats

The theory that dietary fats are completely hydrolyzed by pancreatic lipase to glycerol and fatty acids before absorption has been challenged by Frazer.[49] According to this lipolytic theory, stated by Munk in 1890, the products of hydrolysis pass through the gut wall as glycerol and soaps of the fatty acids and are resynthesized into fats chiefly by the liver. Vérzàr amended this to state that the fatty acids are transported across the gut wall as complexes with bile salts and that the resynthesis of fats occurs in the gut wall. Frazer showed that fats are hydrolyzed only 40 to 60 per cent by lipase in vitro under conditions comparable to those in the gut and that negatively charged particles 0.5 microns in diameter are readily absorbed whatever sort of lipid is present.[50] Frazer[49] therefore concluded that lipid was absorbed through incomplete hydrolysis, to monoglycerides or diglycerides, and the formation of triple complexes of fatty acid, monoglyceride, and bile salt, which are absorbed as fine emulsions. Most of the lipid absorbed is carried by the lymphatics; the free fatty acids may be transported by the portal vein. A number of different in vivo experiments using fed, labeled fats have shown that hydrolysis occurs only to about 30 or 40 per cent.

The absorbed fat may be considerably altered before being stored. The fatty-acid carbon skeleton may be lengthened or shortened, and the fatty acid can be saturated or desaturated. Most, if not all, of these

changes in the character of the fatty acids are carried on in the liver. The concept, first stated by Knoop in 1904, that fatty-acid carbon chains are broken down 2 carbons at a time has been amply confirmed by recent experiments with labeled fatty acids.

The oxidation of fatty acids by cell homogenates, isolated mitochondria and finally by soluble enzyme systems has been studied by Kennedy and Lehninger,[51] Green et al.[52] and Drysdale and Lardy.[53] This enzyme system was shown to require DPN, ATP, and Mg^{++}. The most recent studies have revealed that CoA is

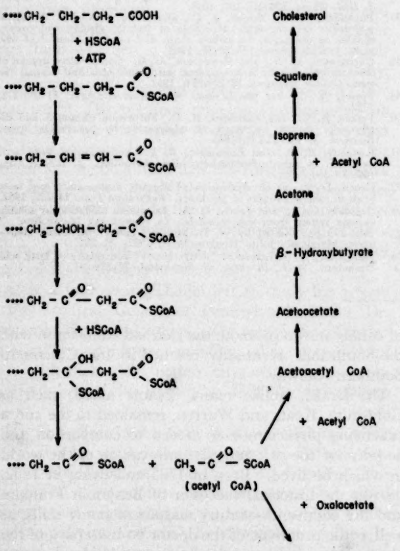

FIGURE 3. *Role of CoA in the Oxidation of Fatty Acids. The acetyl CoA formed may enter the Krebs cycle (see Figure 2), form acetoacetate, beta-hydroxybutyrate and acetone (ketone bodies) or form cholesterol and steroids. The probable path of cholesterol formation via isoprene and squalene is indicated.*

functional in the splitting of the carbon chain and that the 2-carbon compound released in the process is acetyl CoA.[54] The ATP is needed only to get a CoA molecule attached to the carboxyl group of the fatty acid. This activates the molecule so that a second molecule of CoA can attack the beta carbon of the chain and split off the terminal 2 carbons as acetyl CoA (Fig. 3). The main chain is left with a new carboxyl group to which a CoA molecule is attached, so that it is ready for further beta oxidation. In this way a long-chain fatty acid can be split to 2-carbon fragments without the formation of free, intermediate, short-chain fatty acids. The acetyl CoA units produced from fatty acids can combine with oxalacetate to form citrate. The citrate obtained in this way is metabolized as usual in the Krebs cycle (Fig. 2). This is the normal metabolic pathway by which the fatty acids derived from fat are converted to carbon dioxide and water. In the absence of adequate amounts of oxalacetate 2 acetyl CoA units condense to form acetoacetyl CoA in addition to free CoA. The CoA is then split off to yield acetoacetate, which, together with the beta-hydroxybutyric acid and acetone derived from it, constitutes the ketone bodies.

The liver can convert fatty acids to acetyl CoA faster than these acetyl CoA units can combine with oxalacetate to produce citrate and be oxidized in the Krebs cycle. The excess acetyl CoA units condense to form acetoacetate. The liver thus normally secretes ketone bodies into the blood, and these are normally metabolized by muscle and other tissues. In diabetes or starvation the amount of oxalacetate in tissues is reduced, Krebs-cycle metabolism is correspondingly decreased, and ketone-body production is increased. One of the major metabolic sources of oxalacetate is the reaction in which pyruvate is carboxylated to give oxalacetate. Since pyruvate in turn is derived metabolically largely by glycolysis from glucose, carbohydrate deprivation by either diabetes or starvation will result in a decreased availability of pyruvate and oxalacetate.

(To be concluded)

REFERENCES

1. Roe, A., and Albenesius, E. L. Isotope effect. III. Reaction of acetone-1-C^{14} with alkaline hypoiodite. *J. Am. Chem. Soc.* **74**: 2402, 1952.
2. Thorn, M. B. Studies on enzymic oxidation of succinic acid containing deuterium in methylene groups. *Biochem. J.* **49**:602-609, 1951.
3. Racker, E., and Krimsky, I. Mechanism of action of glyceraldehyde-3-phosphate dehydrogenase. *Nature* **169**:1043, 1952.
4. Dickens, F., and Glock, G. E. Direct oxidation of glucose-6-phosphate, 6-phosphogluconate and pentose-5-phosphates by enzymes of animal origin. *Biochem. J.* **50**:81-95, 1951.
5. Smyrniotis, P. Z., and Horecker, B. L. Fixation of carbon dioxide in 6-phosphogluconic acid. *J. Biol. Chem.* **196**:135-142, 1952.
6. Benson, A. A., Bassham, J. A., and Calvin, M. Path of carbon in photosynthesis. XV. Ribulose and sedoheptulose. *J. Biol. Chem.* **196**:703-716, 1952.
7. Bloom, B., Stetten, M. R., and Stetten, DeW., Jr. Evaluation of catabolic pathways of glucose in mammalian systems. *J. Biol. Chem.* **204**:681-694, 1953.
8. Racker, E. Enzymatic synthesis and breakdown of desoxyribose phosphate. *J. Biol. Chem.* **196**:347-365, 1952.
9. Hastings, A. B. Factors affecting metabolism of glucose and pyruvate, in vitro. In *Carbohydrate Metabolism: Symposium on the clinical and biochemical aspects of carbohydrate utilization in health and disease.* 144 pp. Edited by V. A. Najjar. Baltimore: Johns Hopkins Press, 1952. Pp. 59-75.
10. Krebs, H. A. Intermediary stages in biological oxidation of carbohydrate. *Adv. Enzymol.* **3**:191-252, 1943.
11. Ogston, A. G. Interpretation of experiments on metabolic processes using isotopic tracer elements. *Nature* **167**:963, 1948.
12. Stern, J. R., and Ochoa, S. Enzymatic synthesis of citric acid. I. Synthesis with soluble enzymes. *J. Biol. Chem.* **191**:161-172, 1951.
13. Lipmann, F. Biosynthetic mechanisms. *Harvey Lect. Series* **44**: 99-123, 1948-1949.
14. Lynen, F., Reichert, E., and Rueff, L. Zum biologischen Abbau der Essigsäure. VI. "Aktivierte Essigsäure." *Annalen* **574**:1-32, 1951.
15. Novelli, G. D., Gregory, J. D., Flynn, R. M. and Schmertz, F. J. Structure of coenzyme A. *Federation Proc.* **10**:229, 1951.
16. Schweet, R. S., and Chenlock, K. Pyruvic oxidase of pigeon breast muscle. III. Factors influencing enzymatic activity. *J. Biol. Chem.* **199**:749-756, 1952.

17. Hager, L. P., Fortney, J. D., and Gunsalus, I. C. Mechanism of pyruvate and α-ketoglutarate dehydrogenase systems. *Federation Proc.* **12**:213, 1953.
18. Bullock, M. W., et al. Synthesis of compounds in thioctic acid series. *J. Am. Chem. Soc.* **74**:3455, 1952.
19. Reed, L. J., and DeBusk, B. G. Chemical nature of α-lipoic acid conjugate required for oxidation of pyruvate and α-ketoglutarate by *Escherichia coli* mutant. *J. Biol. Chem.* **199**:881-888, 1952.
20. *Idem.* Mechanism of enzymatic oxidative decarboxylation of pyruvate. *J. Am. Chem. Soc.* **75**:1261, 1953.
21. Calvin, M., and Barltrop, J. A. Possible primary quantum conversion act of photosynthesis. *J. Am. Chem. Soc.* **74**:6153, 1952.
22. Martius, C. Sur le mode d'action de la thyroxine. In *Abstracts of Communications of the Second International Congress of Biochemistry, 1952.* 510 pp. Paris, France: Masson, 1953. P. 60.
23. Weil-Malherbe, H. Biological oxidations and reductions. *Ann. Rev. Biochem.* **17**:1-34, 1948.
24. Slater, E. C. Comparative study of succinic dehydrogenase-cytochrome system in heart muscle and in kidney. *Biochem. J.* **45**:1-8, 1949.
25. Lardy, H. A., and Wellman, H. Oxidative phosphorylations: rôle of inorganic phosphate and acceptor systems in control of metabolic rates. *J. Biol. Chem.* **195**:215-224, 1952.
26. McIlwain, H. Phosphates of brain during *in vitro* metabolism: effects of oxygen, glucose, glutamate, glutamine, calcium and potassium salts. *Biochem. J.* **52**:289-295, 1952.
27. Sanger, F., and Tuppy, H. Amino-acid sequence in phenylalanyl chain of insulin. 1. Identification of lower peptides from partial hydrolysates. *Biochem. J.* **49**:463-481, 1951.
28. Sanger, F., and Thompson, E. O. P. Amino acid sequence in glycyl chain of insulin. *Biochem. J. (Proc. Biochem. Soc.)* **52**:iii, 1952.
29. du Vigneaud, et al. Personal communication.
30. Schoenheimer, R. *Dynamic State of Body Constituents.* 92 pp. Cambridge, Massachusetts: Harvard University Press, 1949.
31. Anfinsen, C. B., and Steinberg, D. Studies on biosynthesis of ovalbumin. *J. Biol. Chem.* **189**:735-744, 1951.
32. Sprinson, D. B., and Rittenberg, D. Rate of interaction of amino acids of diet with tissue proteins. *J. Biol. Chem.* **180**:715-726, 1949.
33. Borsook, H., et al. Metabolism of C^{14}-labeled glycine, L-histidine, L-leucine and L-lysine. *J. Biochem.* **187**:839-846, 1950.
34. Siekevitz, P., and Zamecnik, P. C. In vitro incorporation of $1\text{-}C^{14}$ DL-alanine into proteins of rat-liver granular fractions. *Federation Proc.* **10**:246, 1951.
35. Peters, T. Jr., and Anfinsen, C. B. Net production of serum albumin by liver slices. *J. Biol. Chem.* **186**:805-813, 1950.
36. Brachet, J. Metabolism of nucleic acids during embryonic development. *Cold Spring Harbor Symposia Quant. Biol.* **12**:18-26, 1947.
37. Geiger, E. Role of time factor in protein synthesis. *Science* **111**: 594-599, 1950.
38. Chantrenne, H. Requirement for coenzyme A in enzymatic synthesis of hippuric acid. *J. Biol. Chem.* **189**:227-233, 1951.
39. Simmonds, S., Tatum, E. L., and Fruton, J. S. Utilization of phenylalanine and tyrosine derivatives by mutant strains of *Escherichia coli*. *J. Biol. Chem.* **169**:91-101, 1947.
40. Axelrod, A. E. Role of vitamins in antibody production. *Metabolism* **2**:1-8, 1953.
41. Katz, J., Lieberman, I., and Barker, H. A. Acetylation of amino acids by enzymes of *Clostridium kluyveri*. *J. Biol. Chem.* **200**:417-429, 1953.
42. Muir, H. M., Neuberger, A., and Perrone, J. C. Biosynthesis of globin in rat. *Biochem. J. (Proc. Biochem. Soc.)* **49**:lv, 1951.
43. Braunstein, A. E., and Kritsman, M. G. Über den Ab- und Aufbau von Aminosäuren durch Umaminierung. *Enzymologia* **2**:129-146, 1937.
44. Snell, E. E. Summary of known metabolic functions of nicotinic acid, riboflavin and vitamin B_6. *Physiol. Rev.* **33**:509-524, 1953.
45. Shemin, D. Biosynthesis of porphyrins. *Cold Spring Harbor Symposia Quant. Biol.* **13**:185-192, 1948.
46. Bloch, K., and Schoenheimer, R. Biological precursors of creatine. *J. Biol. Chem.* **138**:167-194, 1941.
47. Buchanan, J. M., Sonne, J. C., and Delluva, A. M. Biological precursors of uric acid. II. Role of lactate, glycine and carbon dioxide as precursors of carbon chain and nitrogen atom 7 of uric acid. *J. Biol. Chem.* **173**:81-98, 1948.
48. Christensen, H. N., and Henderson, M. E. Comparative uptake of free amino acids by mouse-ascites, carcinoma cells and normal tissues. *Cancer Research* **12**:229-231, 1952.
49. Frazer, A. C. Fat metabolism. *Ann. Rev. Biochem.* **21**:245-272, 1952.
50. Frazer, A. C., and Sammons, H. G. Formation of mono- and diglycerides during hydrolysis of triglyceride by pancreatic lipase. *Biochem. J.* **39**:122-128, 1945.
51. Kennedy, E. P., and Lehninger, A. L. Activation of fatty acid oxidation by dihydrodiphosphopyridine nucleotide. *J. Biol. Chem.* **190**:361-368, 1951.
52. Green, D. E., et al. Activation of acetate, acetoacetate and fatty acids in soluble extracts of pig heart. *Federation Proc.* **11**:222, 1952.
53. Drysdale, G. R., and Lardy, H. A. Fatty acid oxidation by soluble enzyme system from mitochondria. In *Phosphorus Metabolism.* 2 vol. 775 pp. Edited by W. D. McElroy and H. B. Glass. Baltimore, Maryland: Johns Hopkins Press, 1952. P. 281.
54. Weinhouse, S. Structure of "active acetyl" and theory of fatty acid catabolism. *Arch. Biochem. & Biophysic.* **37**:239-241, 1952.

MEDICAL INTELLIGENCE

DOCTORS AFIELD

Daniel Drake

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ALTHOUGH never far afield from the profession to which he devoted his life Daniel Drake earned a distinction in other endeavors that made him the leading citizen of his adopted city and outstanding among his contemporaries on the western frontier. Pre-eminently a physician, he made his mark as author, editor, educator and public-spirited citizen. He wrote descriptions of medicines and medicinal plants, forests, meteorology and history, as well as a dispassionate analysis of slavery; he taught at six institutions of higher learning, founded two medical schools, a medical journal and a teachers' college and helped establish a lunatic asylum, an eye infirmary and a public library. And in the midst of these activities and a busy practice he found time to plan the Ohio scheme of canals and to promote the railroad connection with the South that eventually resulted in the Cincinnati Southern Railway.

Dr. Drake, unlike many doctors afield, such as Goldsmith, Keats and Warren, remained to the end a practicing physician, ever moved to compassion and activity for the sick and the unfortunate of the world in which he lived. Born in 1785 and dying in 1852, he was the historical successor of Benjamin Franklin and the eighteenth-century masters of many skills, as well as the prototype of the doctor on horseback of the nineteenth century and the erudite, scholarly physician of the twentieth. His life epitomized the rise from obscurity to eminence that the world began to associate with leaders in America — a pattern made familiar by Horatio Alger to generations of youths here and abroad. Ignorant and nurtured in poverty, he nevertheless attained a unique position in Cincinnati, the city of his adoption, which marked the centennial of his death by the establishment of the Daniel Drake Memorial Hospital in honor of the first student of medicine in Cincinnati, the first Cincinnatian to receive a diploma in medicine, the first medical author in the West and a member of the first active faculty of the first medical institution west of the Alleghenies.[1]

He was a child of the western frontier, where he spent his maturity and worked with many of the leading figures of the day. With them he lifted frontier medicine to the level of an exact science and helped mold a raw society into a cultural and scientific center of which the Middle West and the nation at large are

justly proud. Of the eminent residents of the region and the American and foreign visitors to it, he was on more or less familiar terms with many: William Henry Harrison, Henry Clay, Daniel Webster, Harriet Beecher Stowe, Lafayette, Charles Dickens and Harriet Martineau. His fame had become so great that Abraham Lincoln, troubled in mind and body with an obscure ailment, turned to Dr. Drake for advice.[2]

It was in 1800 that Daniel Drake, fifteen years of age, set out for Cincinnati (then Ft. Washington) to study medicine and Latin with Dr. William Goforth, the leading physician of the struggling village and surgeon general of the Northwest Territory. In later years the boy's adieu to his father was described as follows: "Father remained a day, when to my dismay, he took leave of me, and I took to *Chesselden's* [*sic*] Anatomy."[3] His previous training had included no preparation for the taxing studies he faced: his days had been spent mainly in spinning and dyeing for his mother and helping his father clear the land and work their farm on the Ohio River in Kentucky. Four years of study brought him to the point where he could become Dr. Goforth's partner—perhaps not so much a tribute to his scientific equipment as an indication of the scarcity of doctors in the West.

After a year young Daniel left to study for a term at the Medical College of Pennsylvania under Dr. Benjamin Rush and others. He returned to Cincinnati and set up his own practice, whose growth kept pace with that of the community, which was fast expanding into a city, so that by 1807 he was able to marry.

His first effort in the field of letters, less than seven years after he arrived to study with Dr. Goforth, was an account of epidemic diseases on the frontier.[4] This was one of a series of works on scientific and allied subjects that culminated in the book for which Drake is principally remembered, his description of the diseases of the Mississippi Valley.[5] In 1810 his *Notices Concerning Cincinnati, Its Topography, Climate and Diseases* was published, containing, among other data, a report of "milk sickness," a disease not previously described. This was followed, in 1815, by a careful account (and principal record) of prehistoric mounds formerly existing on the site of the city, with a description of medicinal plants and the characteristics of the forest, a presentation of meteorologic data and a historical note on the settlement of Cincinnati.[6]

But Drake's main interest at this time was the improvement of medical education and practice in his section of the country. To equip himself as a teacher he went to the Medical School of the University of Pennsylvania, which awarded him his medical degree. His first teaching position was in the medical department of Transylvania University, the first medical college in the West.

This preoccupation with the advancement of medical science inspired him, after a period of teaching at the University of Louisville, to plan a medical college in the rapidly growing community on the Ohio River. He obtained a charter from the Ohio General Assembly and established, with the help of sympathetic colleagues, the Medical College of Ohio, of which he was president and in which he was also professor of the institutes and practice of medicine. The pattern of his future life was set with the inauguration of this ambitious project, with which he was associated, off and on, for the rest of his days. Unfortunately, some of the unhappiest events of his career were connected with the institution of which he was the inspiration and founder.

For, with the emergence of his many and great gifts, Drake began to manifest some difficulties of temperament that, in combination with the jealousy and vindictive spirit of several colleagues, led to a series of disastrous quarrels. In his devotion to his ideals of medical education he was apt to be too rigidly uncompromising, with the result that he often found himself thwarted in even the most logical schemes. The ensuing strife led to frequent moves from one school to another. His goal of a graded curriculum with guaranteed salaries for teachers—a unique idea in his day —was eventually attained, but only after recrimination and feuds had embittered much of his life.

Thus, in 1822, he was expelled by the Faculty. And, though the indignant residents of Cincinnati caused him to be reinstated, he immediately resigned, accepting his former professorship of materia medica at Transylvania University, where he later became dean of the medical faculty. He resigned in March, 1827, and returned to Cincinnati, where he established an eye infirmary, thus becoming the first physician west of the Alleghenies to specialize in ophthalmology. In 1828, with Dr. Guy W. Wright, he founded the *Western Medical and Physical Journal*, which he edited.

His interest in medical education continued. He accepted the professorship of the theory and practice of medicine at Jefferson Medical College in Philadelphia, 1830-31. His schemes for the ideal plan of medical teaching led to the establishment, in 1835, of the medical department of Cincinnati College (after an interval during which he returned to the Medical College of Ohio at the urgent request of the trustees, more bickering and machinations by his adversaries on the faculty causing him to resign again in 1832). The Cincinnati College flourished until 1839, when the activities of Drake's opponents in Cincinnati and the opening of the Louisville Medical Institute diminished both the need for the College and its attraction to medical students, so that it was suspended.

Drake accepted a professorship at the Louisville Medical Institute but continued his residence in Cincinnati from April to October of each year. At the same time he traveled through lower Canada and the Mississippi Valley in search of material for his monumental work, referred to above, on the diseases of that area,[5] which was widely read (and widely praised)

both in this country and abroad. Meanwhile, the condition of the Medical College of Ohio had become so critical that Drake's support was asked. He returned, briefly, to the faculty, but intrigues and quarrels again disgusted him, so that he resigned. After a session at the University of Louisville, 1850-52, he accepted, for the fourth time, a professorship at the medical college he had founded. He was a member of the faculty at the time of his death.

Drake never abandoned either his practice or the elevated conception of it that helped him withstand the trials of personal and public feuds and disloyalties. His description of the attributes of the ideal physician is as pertinent today as it was in the early nineteenth century:

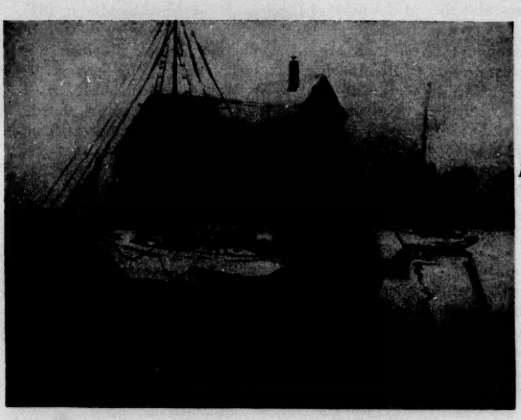
> . . . the only capital of a young physician is his reputation for professional learning, diligence and fidelity. On this character he should place his sole reliance. All his efforts should be directed to its establishment; and whatever can interfere, with this important and difficult object, should be studiously avoided.[5]

Some of the more significant activities of this remarkable man, in addition to those connected with his profession, were involved with the Cincinnati Lyceum, the Circulating Library of Cincinnati, the School of Literature and Arts, the Lancastrian Seminary and the Western Museum, all of which he helped found. He was, for a time, one of the trustees of the Corporation of Cincinnati, a vice-president of the Humane Society and an honorary member, among others, of the Massachusetts Medical Society. His *Letters on Slavery* and the collection of his letters, *Pioneer Life in Kentucky*, are prized for their stylistic charm and their instructive picture of a society that has disappeared from the American scene.

His life was exemplary in the extreme. His own words, spoken shortly before his death at a memorial tribute to Daniel Webster, with whom he had had a friendship of twenty-five years' standing, could equally be applied to Drake himself: "To the example of the mightiest intellect of the age, let me point those who have thought religion not meet for men of culture and genius."[7]

References

1. Horine, E. F. Cincinnatian unique: Daniel Drake. *Cincinnati J. Med.* 33:201-210 and 222-238, 1952.
2. Beveridge, A. J. *Abraham Lincoln: 1809-1858.* 2 vol. Boston: Houghton Mifflin, 1928. Vol. 1, P. 312.
3. Drake, D. D. *Pioneer Life in Kentucky: 1785-1800.* Edited by E. F. Horine. 257 pp. New York: Schuman, 1948. P. xiii.
4. *Idem.* Some account of epidemic diseases which prevail at Mayo-Lick in Kentucky. *Philadelphia M. & Physical J.* 3:85-90, 1808.
5. *Idem. A Systematic Treatise, Histological, Etiological and Practical, on the Principal Diseases of the Interior Valley of North America, as They Appear in the Caucasian, African, Indian and Eskimoux Varieties of Its Population.* 2 vol. Philadelphia: Lippincott, Grambo & Co., 1850 and 1854.
6. *Idem. Natural and Statistical View, or Picture of Cincinnati and the Miami Country.* 250 pp. Cincinnati: Looker & Wallace, 1815.
7. *Idem.* Quoted by Horine.[1]



Massachusetts Physicians Art Society

28. Motif No. 1

Exhibited at American Medical Association Chicago, 1948

Award of Merit

Oil Painting by

Conrad Nobili, M.D.

Associate in Allergy, Boston Dispensary
Secretary, Massachusetts Physicians Art Society

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40261

PRESENTATION OF CASE

A thirty-year-old woman entered the hospital because of impaired vision in the left eye.

About two weeks before admission, while in otherwise excellent health, she noticed blurring of vision in the left eye, accompanied by bitemporal headache and discomfort on moving the eye. Over the next four days vision in that eye rapidly deteriorated to total blindness; meanwhile, the headache became less severe but persisted in mild degree. There were no other symptoms.

The past history was unremarkable, except for severe generalized headaches and occasional vomiting at the time of menstruation. The family history was noncontributory.

On physical examination the patient was of healthy appearance, and no abnormalities were noted. The left eye was completely blind, with 2 or 3 diopters of elevation of the optic disk, engorgement of the retinal veins and small peripapillary hemorrhages. The visual acuity was normal in the right eye, and the right fundus appeared normal, but there was a defect in the left lower quadrant of the visual field. The left pupil was fixed to direct light but reacted consensually; the right pupil was normal. The ocular movements were normal. The remainder of the neurologic examination was unremarkable.

The temperature was 98.6°F., and the pulse 72. The blood pressure was 120 systolic, 80 diastolic.

Routine examination of the blood and urine was negative, as was the blood Hinton test. Roentgenograms of the chest and sinuses were normal. Skull films, including views of the optic canals, were within normal limits.

Lumbar puncture on the sixth hospital day demonstrated clear cerebrospinal fluid, under a pressure equivalent to 75 mm. of water, which contained no cells; its protein was 65 mg. per 100 cc., the colloidal gold 0011110000, and the Wassermann test negative. An electroencephalogram on the seventh hospital day showed slow-wave activity and diminution of alpha rhythm over the right side of the head posteriorly. An examination of the visual fields four days after the initial test revealed a total left hemianopia in the right eye. On the ninth hospital day she suddenly complained of a feeling of "heaviness" and "numbness" in the left leg. Two weeks after admission it was observed that she had recovered light perception in the right half of the field of the left eye; the left hemianopia in the right eye was as before. Neurologic examination at this time disclosed normal findings otherwise except for generally brisk tendon reflexes, absent abdominal reflexes and a questionably abnormal right plantar reflex. Lumbar puncture on the next day disclosed a pressure equivalent to 250 mm. of water; the cerebrospinal-fluid protein was 78 mg. per 100 cc. On neurologic examination on the sixteenth hospital day, the patient appeared more lethargic than on admission but was easily aroused to full alertness. Both optic-disk margins were blurred. The other cranial nerves and the arms were normal. There was severe weakness of the left leg, with absence of voluntary movements at the ankle and toes. Tendon reflexes were more active in the left leg than the right, but were equal in the arms. The abdominal reflexes were absent. The left plantar reflex was extensor; the right was absent. There was no sensory loss, but pinpricks were abnormally unpleasant over the left leg. A lumbar puncture on the twentieth hospital day demonstrated elevation of cerebrospinal-fluid pressure and protein as on the previous examination; the fluid contained 5 lymphocytes per cubic millimeter. Later that day complete flaccid paralysis of both legs developed, with absent sensation to a level at about the groin. Over the next seven days, the sensory level ascended to the midportion of the chest (the sixth thoracic segment), and urinary retention occurred, requiring catheter drainage. She complained of bilateral sharp pains in a girdle-like distribution around the lower part of the chest. Meanwhile, visual acuity deteriorated in the right eye to ability to count fingers at 1 foot, and there was papilledema of 1 or 2 diopters in the right disk. The left eye was as before, except that the disk appeared paler than previously. There was a left homonymous hemianopia. Neurologic examination showed complete flaccid paralysis of both legs, with absent reflexes, and absent sensation below about the level of the sixth thoracic segment. For the remainder of the hospital stay the paralysis and sensory loss were unchanged. She remained alert, with intact memory and intellect, and was cheerful in spite of the disability. Urinary-tract infection developed and was treated successfully by appropriate drugs. A lumbar puncture on the sixtieth hospital day showed a cerebrospinal-fluid pressure equivalent to 240 mm. of water; the fluid con-

tained 5 lymphocytes per cubic millimeter, with a protein of 196 mg. per 100 cc., colloidal gold of 1111122222 and negative Wassermann test. Vision gradually improved and the papilledema regressed, but the hemianopia persisted unchanged. At the time of discharge, three and a half months after admission, visual acuity was 15/20 in the right eye and 10/200 in the left.

The patient returned home, where she led an invalid's existence. On examination about one and a half years after discharge there was swelling and pallor of the right optic disk, and the left optic disk was flat and pale. She was confused and appeared to be aphasic. Vision, as well as could be determined, was about the same as on discharge. The arms seemed normal, but there was still complete paralysis of both legs, with absent reflexes and total loss of all forms of sensation below the level of the third thoracic segment. Lumbar puncture at this time showed a pressure equivalent to more than 300 mm. of water, with a bloody spinal fluid, and a protein of 400 mg. per 100 cc. When she was re-examined a month later, there was improvement in speech and the mental state. Three months after that, she had a series of convulsions, after which there was severe impairment of speech and paralysis of the right arm. The optic disks at this time were flat, but pale. Two and a half years after leaving the hospital she had a severe clonic convulsion of the right side and was stuporous for about a week. A transient paralysis of the right facial nerve appeared at this time. Two months later she had become virtually speechless and was unware of her surroundings. In addition to the flaccid paralysis of the legs there was now marked spasticity in both arms. She died two weeks after this examination, about four years after admission to the hospital.

Differential Diagnosis

Dr. Frank B. Walsh*: The symptomatology is very complicated and although I have had plenty of time to think it over, I have not come to a completely final decision. The important features of this history I shall summarize. When the first examination was made there was a severe and profound optic neuritis on the left side and definite evidence of involvement of the visual pathways on the right posterior to the chiasm because there was a defect in the lower left quadrant of the right visual field. Therefore, at the very beginning the lesions were bilateral. Vision in the right eye was 20/20, with light perception only in the nasal field of the left eye. At that time an electroencephalogram suggested a lesion in the right posterior hemisphere. The next development after some days was weakness in the left leg and foot, the plantar reflex on the left becoming extensor. Apparently, therefore, she had a progressive lesion in the right hemisphere as well as optic neuritis on the left side at that time. On the twentieth day a flaccid paralysis of both legs developed, with an ascending sensory level that persisted throughout the patient's lifetime. This was not simply a single transverse lesion; there must have been very extensive damage of the spinal cord from the level of the lesion downward. By this time the vision in the right eye had become reduced to counting of fingers so that she had then in all probability a neuritis that started in the left eye and later appeared in the right eye, and yet she remained bright and cheerful in spite of these incapacities. By the sixtieth day in the hospital—and this is an important feature of the case—the visual acuity of the right eye, which had been reduced to counting of fingers, had improved markedly, and that in the left eye was up to 10/200. The visual acuity, therefore, had definitely improved in both eyes, and the improvement was maintained until death. One and a half years after the onset of the trouble she became confused and aphasic so that there is evidence of further cerebral involvement. There had been evidence of involvement of the left and right optic nerves and right hemisphere, and there was now evidence of involvement of the left hemisphere. Later, convulsions and spasticity of the right arm developed. Death occurred four years after admission to the hospital. The vision was said to have remained unchanged.

There was blood in the spinal fluid when it was last examined. It was not stated whether it was free blood, but since the patient had convulsions I do not see that it makes any difference to the discussion. I have purposely left to the last the noteworthy findings in the cerebrospinal fluid. These examinations were made on four occasions. At the time of admission the pressure was equivalent to only 75 mm. of water, and the protein was 68 mg. per 100 cc.; each time the examination was repeated, it was noted that there was a tendency to increased pressure and increase in the amount of protein, but throughout there was a noteworthy absence of cells. This is characteristic of the Guillain–Barré syndrome — with which, however, the symptomatology is not in any way consistent.

The point that struck me about this case was the multiplicity of involvement — the fact that there was cerebral and spinal-cord involvement and a picture in which there was a tendency to improvement in both the vision and the aphasia. Therefore, it seemed to me that this had to fit into the group of demyelinizing diseases. It is difficult to believe that this was Schilder's disease, which does not usually involve the spinal cord; also, in the cases that I have seen, there had been no tendency to recovery. I shall eliminate Schilder's disease. The next possibility that I thought of was neuromyelitis optica, — and incidentally we do not seem to see so many of these cases nowadays, — but the picture that this patient presented did not seem to me to coincide with what I know of neuromyelitis optica. There were too many cerebral in-

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volvements. I am sure that that does not rule it out. To make a long story short I shall pick as the most likely diagnosis disseminated sclerosis. If I am going to be surprised, I shall remind you of the curious dissociation of protein and cell count in the cerebrospinal fluid. I can scarcely figure how this could have been multiple tumors. Nor do I believe, with the history, that it would have been multiple vascular anomalies of any type. Either of those conditions, however, has been known to explain a high cerebrospinal-fluid protein but usually not in the absence of increased cells.

Clinical Diagnosis

Multiple sclerosis.

Dr. Frank B. Walsh's Diagnosis

Disseminated sclerosis (multiple sclerosis).

Anatomical Diagnosis

Diffuse demyelinating and necrotizing opticoencephalomyelopathy.

Figure 1. *Low-Power Cross-Section Views of the Spinal Cord (Loyez Myelin Stain).*
A=fourth cervical segment, showing secondary ascending and descending tract degeneration, involving the fasciculus gracilis, lateral corticospinal tracts and spinothalamic and spinocerebellar tracts.
B=first thoracic segment, showing asymmetrical myelin degeneration, extending beyond the confines of specific fiber tracts; this appearance is typical of multiple sclerosis.
C=eighth thoracic segment; the cord is destroyed and is represented by a thin ribbon of tissue; the black circles are prominent blood vessels. The posterior roots (a) *are intact, and the anterior roots* (b) *are degenerated.*
D=lumbosacral region, with the cauda equina. The cord is the shapeless structure in the center, surrounded by roots, some intact and others degenerated.

Dr. Edwin B. Dunphy: Are there usually cells in the cerebrospinal fluid with Schilder's disease? Does it occur in children?

Dr. Walsh: Yes; there is usually an excess of lymphocytes. The diagnosis of Schilder's disease, in my experience, is usually made at autopsy. I have seen it more frequently in children than in adults. I have seen it with marked elevation of the intracranial pressure on several occasions. I have not satisfied myself that optic neuritis occurs in Schilder's disease. It probably occurs in some cases, but I have not noted it in the cases that I have seen.

Pathological Discussion

Dr. Edward P. Richardson, Jr.: We are all very grateful to Dr. Walsh for a most lucid and interesting discussion of this remarkable case. Before going on immediately to consider the diagnosis, I should like to present the pathological findings, with a few illustrations. In the first place there was severe disease of the spinal cord. This was apparent on gross examination, for in the upper thoracic region the cord tapered off abruptly in diameter and in the midthoracic region and below became a thin, shriveled

ribbon, which was no longer truly recognizable as spinal cord but to which normal posterior roots were attached.

FIGURE 2. *Low-Power Cross-Section Views of the Optic Nerves Just Anterior to the Chiasm (Loyez Myelin Stain). In* A *(left) the degeneration is slight, but most marked in the central region. In* B *(right) there is prominent central and peripheral demyelination.*

Microscopically, the upper cervical cord showed ascending and descending fiber-tract degeneration (Fig. 1*A*), indicating severe disease above and below these segments. In the lower cervical and upper thoracic regions there was extensive loss of myelinated fibers in an asymmetrical distribution that could not possibly be interpreted as secondary tract degeneration, but indicated an intrinsic lesion at these levels (Fig. 1*B*). Although there was severe destruction of axis cylinders as well, a few remained even where myelin sheaths had wholly disappeared. Beginning at about the fourth thoracic segment, there was degeneration of gray matter as well as of myelin, and this increased in severity as lower levels were reached until, in the mid-thoracic region and below, virtually the entire cord was destroyed (Fig. 1*C* and *D*), leaving only a shapeless mass containing dense gliosis, scattered collections of microglial phagocytes and a very few irregularly distributed, still intact nerve fibers. In these regions of greatest destruction the posterior roots were normal because of preservation of the nerve-cell bodies in the spinal ganglions, but the anterior roots were degenerate. These findings explain well the complete and persistent flaccid paraplegia and the loss of all forms of sensation below the upper thorax that were observed clinically. The pathologic process likewise affected the optic nerves (Fig. 2*A* and *B*), more severely on the right, where the destruction of axis cylinders was also relatively less than that of myelin sheaths, which doubtless accounts for the good recovery of vision that the patient experienced. As in the spinal cord the lesions appeared old, without evidence of recent activity.

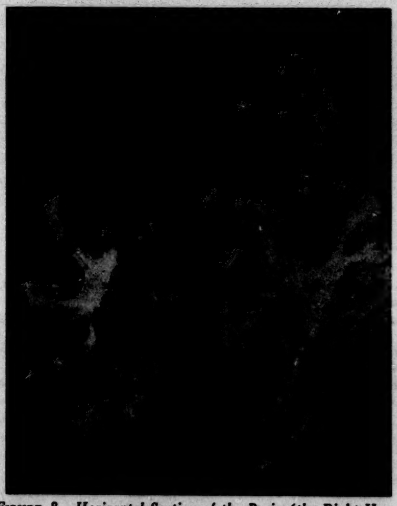

FIGURE 3. *Horizontal Section of the Brain (the Right Hemisphere Appears on the Left).*
The principal demyelinative lesions are outlined by arrows. Note also the multiple cavities, indicating a severe destructive lesion, in the corpus callosum.

In the brain there was extremely severe and extensive disease of the white matter affecting both hemispheres to a nearly equal degree (Fig. 3 and 4). Above the horizontal plane of the lateral ventricles almost the entire central white matter was affected. At lower levels the lesions were mostly in the frontal lobes and corpus callosum. There was, in addition, a discrete lesion in the right occipital lobe, involving the optic radiations in the vicinity of the calcarine cortex. There were no noteworthy changes in the cerebral cortex itself, nor in any of the central gray masses. The lesions in the more anterior regions of the brain contained large numbers of fat-filled phagocytes, along with numerous, very large, swollen astrocytes,—and many perivascular collections of lymphocytes,—indications of relatively recent activity, whereas the lesions in the right occipital lobe appeared much older. As with the lesions elsewhere there was relative sparing of axis cylinders. The cerebellum and brain stem were entirely free of lesions, except for bilateral corticospinal-tract degeneration secondary to the fiber

destruction in the cerebral hemispheres above. These changes in the brain can be related to the mental symptoms and the additional neurologic abnormalities that appeared after the patient had left the hospital. Although the cortex appeared intact it is assumed that the process, as it approached the cortex, brought about alterations in neuronal function, giving rise to the convulsions that occurred intermittently in the later stages of the illness. Furthermore, these extensive cerebral lesions can be held to account for the repeatedly observed elevation of spinal-fluid pressure.

On the basis of the pathological findings it is difficult to classify this case among the well recognized terms applied to the various entities that come under the larger group of demyelinating diseases.* The objections to subclassifying this condition have already been pointed out by Dr. Walsh. On the basis of the brain lesions alone one could call this "Schilder's disease" in view of the very extensive coalescent white-matter lesions of both cerebral hemispheres, much larger than the usual cerebral lesions of multiple sclerosis. However, the changes in the lower cervical and upper thoracic portions of the spinal cord are entirely typical of classic multiple sclerosis, of which the optic-nerve lesions are also typical. On the other hand the lower half of the cord was involved in an intense necrotizing process that was by no means confined to the white matter but destroyed the entire gray matter as well. If one had seen only the lesions of the optic nerves, together with necrotizing disease in the cord, the condition could then have been classified as "neuromyelitis optica." This case is therefore important as representing a diffuse demyelinating and necrotizing encephalomyelopathy with optic-nerve involvement that belongs in the large group of the demyelinative diseases and yet cannot be brought under any one of the subclassifications of that group.

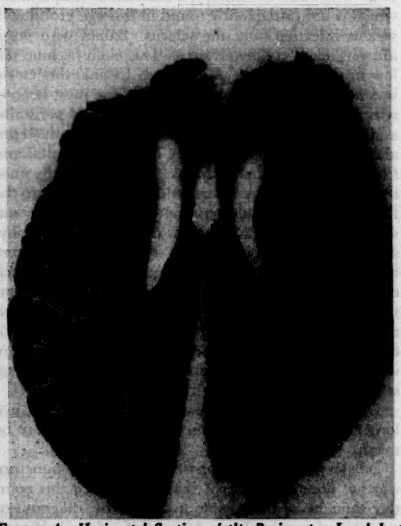

FIGURE 4. *Horizontal Section of the Brain, at a Level Just Including the Tops of the Lateral Ventricles (Loyez Myelin Stain), the Right Hemisphere Appearing on the Right. The lesions stand out clearly against the darkly stained normal white matter.*

*Adams, R. D., and Kubik, C. S. Morbid anatomy of demyelinative diseases. *Am. J. Med.* 12:510-546, 1952.

CASE 40262

PRESENTATION OF CASE

A two-week-old male infant was referred from another hospital because of refusal to take his formula.

The patient was delivered two weeks before term by cesarean section because of cephalopelvic disproportion and prolonged labor during the delivery of the mother's first child. The birth weight was 6 pounds, 4 ounces; he cried spontaneously. After an initial weight loss he regained his birth weight before discharge from the hospital eight days later. The circumcision wound healed readily. He took a formula of evaporated milk, Karo syrup and water with added vitamins at four-hour intervals and finished most of each feeding. The stools and urine were normal. At six o'clock the night before admission he appeared fretful, refused all oral feeding and spat up the small amount of fluid offered. He had a normal stool then and on the morning of admission. He continued to be fretful and at noon was taken to the other hospital, where his pediatrician found a subnormal rectal temperature, a distended abdomen with no peristalsis and tachypnea. A roentgenogram of the chest revealed "clear lungs and a normal-sized heart." Roentgenograms of the abdomen showed gas in the stomach, small bowel and colon but none in the rectosigmoid. There were no fluid levels. A saline enema resulted in clear fluid. He was referred to this hospital for further management. The father thought the patient had lost weight in the last few days and had a yellow tint to his skin.

The mother's pregnancy had been uneventful, and the cesarean section uncomplicated. A six-year-old sister was well.

On physical examination the patient was small, thin and undernourished and cried with a good volume. He weighed 5 pounds, 6 ounces. The skin had a yellow tint, and there was yellowness of the scleras. The head was normal, with slightly depressed fontanelles. The eyes, ears, nose and throat were not remarkable, and the mouth was dry. The neck was supple, and the lung fields were clear to percussion and auscultation. The heart was not enlarged, and no murmurs were heard. The abdomen was tense, moderately dis-

tended and diffusely tympanitic; no peristalsis was heard. The umbilicus was well healed. The liver edge was palpable 2 or 3 fingerbreadths below the right costal margin and was firm and nonpulsatile. The spleen was palpable 2 fingerbreadths below the left costal margin. The left kidney was palpable in the left flank below the spleen. The genitalia and extremities were normal.

The temperature was 97.6°F. by rectum, the pulse 140, and the respirations 60.

The urine appeared grossly purulent and gave a + + test for albumin and a + test for sugar; the sediment was loaded with neutrophils and gram-positive bacilli. Urine culture grew out *Escherichia coli*. Examination of the blood revealed a white-cell count of 34,000, with 66 per cent neutrophils, 27 per cent lymphocytes and 1 per cent monocytes, and a hemoglobin of 15.3 gm. per 100 cc. The sodium was 132 milliequiv., the potassium 7.5 milliequiv., the carbon dioxide 6.4 milliequiv., and the chloride 111 milliequiv. per liter; the total protein was 6.7 gm., and the nonprotein nitrogen 195 mg. per 100 cc. An electrocardiogram gave no evidence of hyperkalemia. An x-ray film of the chest showed no consolidation in the lungs.

An ankle vein was catheterized, and administration of a solution of three parts 5 per cent dextrose in water, two parts 0.85 per cent sodium chloride and one part one-sixth molar solution of lactate was started. The patient was placed in an incubator with oxygen. Streptomycin, 150 mg., and aqueous penicillin, 300,000 units, were given intramuscularly, and 1,000,000 units of penicillin was put into 1 liter of the intravenous solution. After seven hours he had received 325 cc. of the intravenous solution and appeared well hydrated. He voided twice and the urine again appeared purulent. The temperature remained 97°F. Fourteen hours after admission he spat up dark-brown material, which was guaiac negative on several tests. A thin polyethylene catheter was passed into the stomach, and 15 cc. of similar material, with about 50 cc. of gas, was obtained. The temperature was 103°F. The abdomen was distended and tympanitic, and peristalsis absent. He was voiding well, however, and he was given 250 mg. of sulfadiazine intravenously and an additional 500 mg. was put into the solution. "Twitching of the upper extremities thirty to forty seconds in duration," was noted; 2.5 cc. of calcium gluconate was added to 250 cc. of the solution. About twenty hours after admission, after he had received 600 cc. of fluid intravenously, the blood hemoglobin was 10.3 gm., and the pH of the blood was 7.28; the serum nonprotein nitrogen was 138 mg., and the calcium 5.0 mg. per 100 cc., and the carbon dioxide 13.6 milliequiv., the potassium 7.2 milliequiv., and the sodium 122 milliequiv. per liter. The patient's skin was leathery and tinted yellow; the chest was clear, and the abdominal findings as before. The temperature was 97°F., the pulse 102, and the respirations 28 per minute. He cried with short, sharp wails. He continued tachypneic and twenty-six hours after admission his heart stopped. Resuscitative measures failed.

Differential Diagnosis

Dr. Gertrud C. Reyersbach*: The history is more typical of the patient's age group than of any particular disease. Babies in the newborn period may be quite seriously ill but behave fairly normally; often they have no fever. For a few days this child did not gain weight and became slightly yellow; then he showed quite dramatically how ill he was by refusing feedings, becoming fretful and having a distended abdomen. I should guess that the physician who saw him in the outside hospital thought that the child had an overwhelming infection. There were several things to go with this: the history, a subnormal temperature, which is not infrequently found in this age group with serious infection, and the icterus. Babies with sepsis are very likely to have icterus. This child became yellow in the second week of life so I think the icterus was not that of the neonatal period. The most striking symptoms were in the abdomen: absence of peristalsis and distention. These are compatible with sepsis alone. When the child came into this hospital and further data became available, other thoughts must have crossed the physicians' minds. In addition to the findings in the outside hospital an enlarged liver and spleen were found, and he was dehydrated. The physicians in this hospital found signs of infection very readily: the patient voided purulent urine, which contained *Esch. coli*. The white-cell count was considerably elevated. Incidentally, for a patient of this age he showed a very good response of polymorphonuclear neutrophils. I wonder whether a blood culture was taken with the possibility of an overwhelming septicemia in mind.

Dr. Benjamin Castleman: The child did not live long enough after admission for a blood culture to be taken.

Dr. Reyersbach: Apparently a lumbar puncture was not done either. So I shall abandon at this point the thought of being able to prove the diagnosis of generalized sepsis. I wonder also if a blood Hinton test was done.

Dr. Castleman: No.

Dr. Reyersbach: The patient had evidence of dehydration clinically and also signs of electrolyte imbalance indicated by the chemical determinations that were done on admission, the most striking of which was the nonprotein nitrogen of 195 mg. per 100 cc. Did he have intrinsic disease in the kidneys, with the result that he was not capable of excreting what he should, or was this prerenal azotemia? The problem is partially solved by the result of intravenous therapy, which caused the nonprotein nitrogen to drop from 195 mg. to 130 mg. per 100 cc., indicating that the kidneys could work in spite of the fact that there seems to have been overwhelming infection in them.

*Associate physician to Children's Medical Service, Massachusetts General Hospital.

I shall pass over the green test for sugar in the urine, for I do not find that it is of any importance. Was a test for bile in the urine done on this jaundiced baby?

DR. CASTLEMAN: No.

DR. REYERSBACH: I suppose that this was not done because the urine was grossly free of bile. With the jaundice of septicemia there is often no bile in the urine. An attempt was made to treat the dehydration and correct the deranged electrolytes. This was successful to the extent that the baby started to void well and appeared better hydrated. The potassium stayed as it was. In the process of hydration the serum sodium was diluted, but I cannot imagine that this had anything to do with the final outcome. At this point I should like to discuss the calcium of 5 mg. per 100 cc., which was actually found terminally. I suspect that the calcium may have been at that level on admission, probably owing to an elevated serum phosphorus level. I think the convulsions were due to the low calcium and started at the point where the marked acidosis present on admission was partially corrected and allowed them to occur. I do not think the chemical data are very helpful in the final diagnosis. Will Dr. Gibbons show the x-ray films?

DR. JOHN F. GIBBONS: These films, made in the other hospital, are typical of ileus in the abdomen, with gas in the stomach, throughout the small bowel and in the rectum and rectosigmoid. The liver appears enlarged, extending down to the pelvis, and the spleen is, I should guess, at the top limit of normal size for an infant. The lungs look clear, and I cannot make out the kidney shadows because of the gas in the bowel.

DR. REYERSBACH: Is there any reduplication of the bowel that you can see?

DR. GIBBONS: There are no masses that suggest duplication in the bowel, and no gas-filled bowel that is obviously extra.

DR. REYERSBACH: Do you think that the diaphragm could have pushed the liver down?

DR. GIBBONS: Both leaves of the diaphragm are quite low, but I suspect that the liver is enlarged.

DR. REYERSBACH: And there is definitely nothing abnormal in the chest?

DR. GIBBONS: That is correct.

DR. REYERSBACH: Can you see the kidneys?

DR. GIBBONS: No.

DR. REYERSBACH: The bones are perfectly normal?

DR. GIBBONS: Yes.

DR. REYERSBACH: When I read the protocol, I was impressed by the intestinal obstruction and wondered what its cause was. Whenever there is intestinal obstruction in the first day or two of life one has to think of meconium ileus or intestinal atresia or stenosis. This child did not have any of these. Intestinal obstruction in the second week of life might result from duplication of the gut, malrotation of the cecum or an annular pancreas. Such obstructions ought to cause more dramatic symptoms such as vomiting. I went over the record carefully: once the baby spat up at home; he spat up something he did not want to eat; he also vomited once in the hospital; that seems to be very little vomiting for an acute obstruction. Dr. Gibbons has helped me by saying that he cannot see a duplication. Certainly, an annular pancreas is ruled out by the x-ray films. I suppose that one cannot rule out a malrotation of the bowel.

DR. GIBBONS: I do not think that it can be ruled out. It may or may not be helpful to add that I cannot locate gas in the large bowel above the rectosigmoid area; only on looking at the lateral projections can I say that there is gas down there because there is gas immediately anterior to the coccyx and sacrum.

DR. REYERSBACH: It seems to me that there is one proved diagnosis, pyelonephritis due to *Esch. coli*, in a newborn infant. According to the protocol there was no obvious portal of entry. The circumcision wound was said to be well healed, and the umbilicus looked all right. Where did he get the *Esch. coli* infection? The children—all boys—with pyelonephritis whom we have seen also had congenital abnormalities in the kidneys. Since we cannot see the kidneys I can only guess that he too probably had a congenital abnormality of the kidney; I do not know what the abnormality was.

The next question is whether the sepsis of the kidneys explains the complete other picture. I think it does. After looking at the x-ray films today I believe the patient had ileus secondary to infection. I think the icterus can be explained by infection. I am afraid that I cannot explain the large liver. In the absence of blood cultures a diagnosis of septicemia cannot be made.

DR. ALLAN M. BUTLER: From the notes in the record the house staff thought this child had sepsis and pyelonephritis, *Esch. coli* being the infective organism. Also, there was a question about an abnormality of the gastrointestinal tract and obstruction. We shall be interested to learn whether they were correct in deferring a diagnostic paracentesis or further diagnostic procedure hoping that parenteral administration of fluids and chemotherapy would so improve his condition as to clarify the diagnosis or permit an exploratory operation if indicated.

CLINICAL DIAGNOSES

Neonatal sepsis.
Pyelonephritis.
Ileus.

DR. GERTRUD C. REYERSBACH'S DIAGNOSES

Pyelonephritis (*Esch. coli*).
Ileus.
?Congenital abnormality of kidney.
?Septicemia due to *Esch. coli*.

Anatomical Diagnoses

Bronchopneumonia, severe, with abscess formation (Esch. coli).

Pyelonephritis, acute (Esch. coli).

Pathological Discussion

Dr. Castleman: At autopsy the most strikingly abnormal organ was the kidney. Normally, the combined weight of both kidneys in a child of this age is about 22 gm.; in this child they weighed over 40 gm., or twice the normal weight. When they were cut across, the absence of the normal sharp demarcation between cortex and medulla, the hemorrhagic medulla and the edematous cortex indicated that there was infection in these kidneys. On microscopical examination both cortex and medulla were infiltrated with a cellular exudate that contained predominantly polymorphonuclear leukocytes; in many places there were numerous abscesses.

The lungs also were not normal. There was a great deal of pneumonia throughout both lower lobes and the right middle lobe. Some of it was destroying the alveolar walls, with abscesses in places. It seemed to me that the process had been going on perhaps longer than the kidney infection although I cannot be sure of that. I believe that the infection started in the lungs as a pneumonia and that this was followed by a bacteremia and infection of the kidneys. There was no abnormality or obstruction anywhere in the entire genitourinary tract, so that I believe we can rule out an ascending infection and assume that the process was hematogenous. Of course, one cannot be absolutely sure that it did not start in the kidney and that the pneumonia was secondary, but more often it is the other way around. I believe it would have been easier for the child to pick up a respiratory infection. Cultures of both the lung and the kidneys showed *Esch. coli*. The liver, except for some fatty change, was not abnormal and was not really enlarged, so that I think Dr. Reyersbach's idea that the lungs pushed the diaphragm down is correct.

Dr. Gibbons: Do you know how long before death these chest films were taken?

Dr. Castleman: One day before death.

Dr. Gibbons: It is hard for me to conceive that there was much pneumonia in the lungs at the time the films were taken. I wonder if it was possible that most of the pneumonia developed terminally. These lungs look very clear to me in both the anteroposterior and lateral views; there are no visible consolidated areas that are larger than a few millimeters, at any rate.

Dr. Castleman: That may be evidence that the pyelonephritis was primary and the pulmonary infection secondary.

Dr. Gibbons: The protocol repeats that the lungs were normal on physical examination.

Dr. Castleman: We found a great deal of pneumonia, and there was practically no air in either lower lobe at the time of autopsy. The infection may have been aggravated just before death.

The abdominal cavity was perfectly normal. There was no anomaly.

Dr. Reyersbach: Was a post-mortem blood culture done?

Dr. Castleman: No.

Dr. Gibbons: Dr. Castleman, can you postulate the possibility of a retrograde infection secondary to the circumcision?

Dr. Castleman: The circumcision site looked perfectly clear, as did the umbilicus. I think we have to assume that the infection was hematogenous, and we shall have to leave it up in the air whether the process started in the lung and went to the kidneys or the other way around. At first I favored its starting in the kidneys until I saw some evidence in the lungs of an older process with phagocytes and large monocytes, which certainly were more than a few days old.

Dr. Gibbons: I cannot get away from the very clear lungs. I should be willing to swear that when these films were made there was no pneumonia. I think the pneumonia must have been secondary if there was infection at that time.

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INTERLINGUA

MANY efforts have been made over the years, some of which have been spontaneous and relatively successful and some deliberately planned, to overcome the confusion that resulted when the aspirations of a few willful men at the Tower of Babel were repulsed. Of the artificial international languages devised to overcome the speech barrier the most currently popular appears to be Interlingua. Interlingua, composed of elements found in numerous languages, "is understood at sight by anyone trained to read technical material in one of the major languages of the Western World."

When first flushed, a covey of sentences in Interlingua looks like a quick hybridization of French, Spanish and Italian, which is about what it is; but the reader of English with only a smattering of ignorance pertaining to these languages finds that he can translate the lines almost smoothly and absorb their apparent meaning. Thus, from the conclusion of a paper on closed pneumonolysis: *In omne casos de pneumothorace ineffective a causa de adhesiones, thoracoscopia es indicate pro determinar le applicabilitate de pneumonolyse.* One need not be a thoracic surgeon to catch the drift; to write the Interlingual lingo one would obviously have to be a student of it. Certain American journals are exploring the merit of publishing abstracts in Interlingua. Among those that have already adopted it are *Blood, Journal of Dental Medicine* and the *Quarterly Bulletin of Sea View Hospital.*

Of the so-called international auxiliary languages, lingua franca (language of the Franks), in common use in Mediterranean ports, is a natural hybridization of Italian, French, Spanish, Greek and Arabic. Any such hybrid employed as a commercial tongue may be so classified. Thus lingua criola or Creole language is applied to the Portuguese-Negro dialects of Brazil and Portuguese Africa, including the Cape Verde Islands.

A lingua franca familiar to travelers in the Orient and those who read their books and stories is pidgin English. Pidgin is a Chinese corruption of business; the language is a jargon consisting mainly of English words arranged after Chinese syntax.

To pursue the subject to its end, bitter or otherwise, an international auxiliary language is defined by Webster as "Any natural or artificial language used or designed for international intercourse." Latin was the international language of scholarship through the Middle Ages and is still that of the Roman Catholic Church. French has been the international language of diplomacy, at least during the silk-hat era, and English is still that of commerce.

Those who have regarded Esperanto as man's supreme effort to adopt a common tongue may be chastened to learn that over 100 artificial languages have been devised, characterized generally by "phonetic spelling, by simplicity and regularity of syntax, forms, and word derivation, and by freedom from idiomatic phrases." Most important among them are Volapük, Esperanto, Interlingua, Ido, Nov-Esperanto, Arulo, Ro and Novial.

Volapük or Volapuk, literally, world speech, once widely used, is based largely on English. It was invented by Johan Martin Schleyer, of Baden, about 1879. Esperanto, perhaps the best known and one of the most practical, was devised by a Russian, Dr. L. Zamenhof, about 1887. Phonetically spelled it is based on words common to the chief European languages. Interlingua, or Latino sine flexione, was devised by Peano, of Turin, Italy, in 1903.

Ido, an offspring of Esperanto, was invented by de Couturat, Jespersen and others in 1907. Nov-Esperanto, another modification, made its appearance in 1925, the same year in which Arulo was devised by M. Talmey, of New York. Ro, the only a priori language of the present century, was developed by the Rev. Edward P. Foster, of Marietta, Ohio, about 1906. Rejecting all existing words and roots, it is based on the

analysis and classification of ideas—a laudable ambition for any attempt at creating a language. Novial, another venture of Jespersen, of Copenhagen, was brought forth in 1928. It is described as "international in vocabulary, simple in grammar and phonetic in system."

For no particular reason, one is reminded of the invitation extended by the incoming president of the World Medical Association to the delegates then meeting in London, to gather in Athens in the following year. It would simplify matters, he suggested, if they would spend the intervening months in learning Greek.

BED-END MANNER

A peripatetic correspondent of the London *Lancet*, engaged in the usual running commentary to which these traveling scribes are dedicated, has commented with some feeling on the "decline of that fine old medical institution, the Bedside Manner." Of equal significance he finds the rapid and insidious rise of its usurper, the "Bed-end Manner."

In a catalogue of manners one so identified is a product not merely of hospitals per se, but of the modern usages of these institutions. It is characteristic of the Grand Round and sometimes incidentally of the Grand Manner — of the mass approach that "effectively prevents any single doctor from speaking confidential and comforting, if highly unscientific, words to the patient." It represents the final stage in the evolution of a sick person from a patient to a case.

Various factors have contributed to this metamorphosis, which, in England at least, seems to be most closely identified with the teaching hospital. Here, where the patient has become, in a way of speaking, practically an untouchable, history taking has been reduced to the level of a questionnaire in the hands of a student; examination of the heart by such overt methods as percussion and auscultation (it is suggested) has given way to a study of the recordings of the electrocardiograph and the electrophonograph; the barium meal and other forms of roentgenologic exploration have rendered abdominal palpation unnecessary; and chemical determination of the contents of the various fluids of the body and of its excreta, taken in conjunction with a study of the electric waves set in motion by the processes of cerebration and a pursuit of the isotopes, has put into the category of superfluous business all other contacts with the patient, at least by the higher service echelons.

Personal encounters, according to the allegation, are no longer essential above the level of the laboratory technician or even that of the purveyor of food on the one hand and the excretory pan on the other. And the latter may soon be relegated to the limbo of unnecessary utensils since the discovery that more foot pounds of energy per patient are required to utilize this vessel than to walk to the toilet.

WHO TO MEET IN MEXICO

THE World Health Organization, convened at Geneva in May in its seventh annual assembly, voted to hold the eighth assembly in Mexico City next year. This will be the second time only that the assembly will have met other than at the headquarters of the Organization in Geneva, the previous occasion having been at Rome in 1949.

The Mexican Government had offered to bear all additional costs entailed in holding the assembly away from Geneva and to extend to all delegates, observers and other participating persons the necessary facilities, immunities and privileges.

The seventh assembly, under the presidency of Dr. Joseph Nagbe Togba, director of public health and sanitation of Liberia, was attended by delegations from 71 member countries. As part of his report for 1953 the director-general, Dr. M. G. Candau, reviewed 330 public-health projects to which the Organization had given its support, in 74 of the 84 member countries.

These projects included 27 for the control of communicable diseases, the others being for the strengthening of national health administrations, mainly in environmental sanitation, maternal and child health, nursing and social work and occupational medicine, and for the organization of professional and technical education and training.

SPEAKING OF STATISTICS

ADVICES from the resourceful statisticians of the Metropolitan Life Insurance Company indicate that deaths from motor accidents are four times as common in the wild west (say Nevada or Wyoming) as in Massachusetts, and, naturally, that one is ten times as likely to be fatally shot in either of these states as here. It is less easy to understand why residents of the Bay State should fall down twice as frequently as residents of other parts of the country — three times as often, in fact, as the lithe, trigger-happy New Mexican or Carolinian. Even more mystifying is the fact that the death rate from drowning is twice as high in the Land of the Painted Desert as it is in Massachusetts, whose denizens are daily confronted with the hazards of the sea as well as of countless inland lakes and water courses. Obviously, they have never learned to swim in Arizona, but what do they drown in?

One has learned not so much to doubt the validity of statistics as to appreciate the difficulty of interpreting them. It requires wide experience and great knowledge to penetrate into an understanding of the shrouded first causes of these things that are recorded in numbers. All the skill of the chemist, the biologist and the psychiatrist will be needed to explain with equal satisfaction to physicians, smokers and cigarette manufacturers the statistics, for example, on cancer of the lung. Meanwhile conclusions one way or the other must be guarded.

Say what they may of the Blue-law State in regard to the alleged postponement of Thanksgiving in former times, on account of the scarcity of molasses; the voting for Governor Trumbull twelve years after his death, and the whipping of beer barrels for working on Sunday — Connecticut is a noble Commonwealth.

Boston M. & S. J., *July 5, 1854*

MASSACHUSETTS MEDICAL SOCIETY

NEW LAW REGARDING PRESCRIPTION OF HYPODERMIC SYRINGES AND NEEDLES

The Committee on Pharmaceutical Problems, meeting with representatives of the Massachusetts State Pharmaceutical Association, studied the State law regulating the prescription, sale and possession of hypodermic instruments and last year agreed on changes that could be recommended to serve the convenience of patients and physicians and also to eliminate the risk that might occur if essential treatment, such as daily injections of insulin, could not be given immediately because of loss or breakage of a syringe. A new law passed by the State legislature became effective June 16, 1954.

The quadruplicate form issued by the Board of Registration in Medicine will no longer be required. A physician who wishes to have a patient equipped for self-administration of insulin or other hypodermic medication will simply give him an ordinary prescription. This must carry the name and address of the patient, a description of the instruments (syringes or needles or both) and the number required. The pharmacist is authorized to repeat the order, whenever necessary, for a period of a year, unless the physician marks the prescription N.R. (not to be refilled).

It is expected that the new law will eliminate the objections that have existed in the past, and at the same time the new regulations should serve as a safeguard against the abuse of hypodermic instruments.

HENRY M. LEMON, M.D.
CHARLES L. BRENNAN, M.D.
FRANK N. ALLAN, M.D., *Chairman*

DEATH

LINENTHAL — Harry Linenthal, M.D., of Brookline, died on June 10. He was in his seventy-ninth year.

Dr. Linenthal received his degree from Harvard Medical School in 1904. He was a fellow of the American Medical Association and formerly professor of clinical medicine at Tufts College Medical School and physician-in-chief, Beth Israel Hospital.

He is survived by his widow, a daughter and a son.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY, 1954

RÉSUMÉ

DISEASE	MAY 1954	MAY 1953	SEVEN-YEAR MEDIAN
Chancroid	1	4	3
Chicken pox	1569	2579	1865
Diphtheria	7	3	13
Dog bite	1504	1411	1411
Dysentery, bacillary	6	8	5
Encephalitis, infectious	3	2	3
German measles	1045	1577	744
Gonorrhea	168	177	177
Granuloma inguinale	0	0	0
Hepatitis, infectious	110	101	4†
Lymphogranuloma venereum	2	0	0
Malaria	0	1	2
Measles	2853	456	2327
Meningitis, meningococcal	8	15	5
Meningitis, Pfeiffer bacillus	2	5	5
Meningitis, pneumococcal	0	2	2
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	9	5	4
Mumps	2292	1661	1095
Poliomyelitis	5	8	1
Salmonellosis	48	12	11
Scarlet fever	477*	469	519
Syphilis	148	139	188
Trichinosis	2	5	1
Tuberculosis, pulmonary	160	186	203
Tuberculosis, other forms	15	6	15
Typhoid fever	0	3	2
Undulant fever	1	0	2
Whooping cough	194	130	147

*Includes streptococcal sore throat.
†Five-year median.

COMMENT

Diseases below the seven-year median included diphtheria, chicken pox, scarlet fever and pulmonary tuberculosis.

The 1569 cases of chicken pox reported made this the lowest figure for the month of May since 1945.

The 160 cases of pulmonary tuberculosis reported represented a figure that was the lowest for the month of May in the history of this state.

Diseases above the seven-year median were bacillary dysentery, German measles, infectious hepatitis, measles, mumps, poliomyelitis, salmonellosis and whooping cough.

The 6 cases of bacillary dysentery reported represented a slight increase over the seven-year median of 5. However, this disease has shown a sustained decline in incidence since the high point of 96 reported cases in February of this year.

Mumps remained quite high, as indicated by the 2292 reported cases during May. If this trend continues it will offer diagnostic difficulty in certain cases since the meningitis form, which is occasionally seen, can easily be confused with nonparalytic poliomyelitis.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Actinomycosis: Winthrop, 1.

Diphtheria: Boston, 1; Braintree, 1; Fall River, 1; Fort Devens, 1; Framingham, 1; Plymouth, 1; Woburn, 1; total, 7.

Dysentery, bacillary: Boston, 2; Southbridge, 1; Worcester, 3; total, 6.

Encephalitis, infectious: Quincy, 1; Shrewsbury, 1; Worcester, 1; total, 3.

Hepatitis, infectious: Bedford, 1; Belchertown, 1; Boston, 18; Brockton, 5; Cambridge, 18; Chelsea, 2; Chelsea Naval Hospital, 3; Danvers, 1; Fall River, 6; Fort Devens, 3; Franklin, 3; Greenfield, 1; Halifax, 1; Hull, 1; Longmeadow, 1; Lowell, 3; Lynn, 8; Montague, 2; Newton, 1; North Adams, 1; Oxford, 2; Peabody, 1; Plymouth, 5; Quincy, 1; Revere, 1; Somerville, 1; Springfield, 5; Webster, 4; Westboro, 2; Westover Field, 2; Weymouth, 1; Winchester, 2; Worcester, 3; total, 110.

Meningitis, meningococcal: Attleboro, 1; Brockton, 1; Chelsea, 1; Everett, 1; Lowell, 1; New Bedford, 1; Plymouth, 1; Quincy, 1; total, 8.

Meningitis, Pfeiffer bacillus: Boston, 1; Needham, 1; total, 2.

Meningitis, mumps: Lexington, 2; Lynn, 1; Newton, 1; total, 4.

Meningitis, undetermined: Medford, 1; Newton, 1; Palmer, 1; Quincy, 1; Somerville, 1; Springfield, 1; Taunton, 1; Upton, 1; Worcester, 1; total, 9.

Poliomyelitis: Boston, 1; Chelmsford, 1; Fitchburg, 1; Pittsfield, 1; Westfield, 1; total, 5.

Salmonellosis: Beverly, 2; Boston, 8; Brockton, 1; Brookline, 3; Chicopee, 1; Fitchburg, 1; Framingham, 1; Lynn, 1; Newton, 8; Peabody, 7; Plymouth, 1; Quincy, 1; Revere, 4; Sandwich, 1; Somerville, 3; Springfield, 1; Webster, 2; Winchester, 1; Worcester, 1; total, 48.

Tetanus: Fall River, 1.

Trichinosis: Concord, 1; North Andover, 1; total, 2.

Undulant fever: Boston, 1.

CORRESPONDENCE

VETERANS ADMINISTRATION HOSPITALS

To the Editor: The following letter has been sent to physicians living in the part of Massachusetts from which veterans are ordinarily referred to the two Boston Veterans Administration hospitals (the purpose is to call the attention of the physicians of Massachusetts to the fact that both these hospitals are staffed and equipped for the care of eligible veterans with medical and surgical conditions).

Dear Doctor:

The purpose of the present letter is to correct a misconception that appears to exist in the minds of many physicians regarding the function of the Veterans Administration Hospital at West Roxbury, Massachusetts, since its reopening on October 15, 1953. Seemingly, it has not been generally realized that this 304-bed hospital is staffed and equipped to care for veterans suffering from all types of acute medical and surgical conditions.

The West Roxbury Hospital is now affiliated with the Harvard Medical School. Similarly, the Boston Veterans Administration Hospital is affiliated with the Medical Schools of Boston University and Tufts. The Residency Program at the West Roxbury Hospital is integrated with that of the Peter Bent Brigham Hospital, from whose staff it derives many of its Consulting and Attending Physicians.

Thus, Metropolitan Boston is fortunate in having two Veterans Administration Hospitals available for the care of eligible veterans afflicted with acute medical or surgical diseases. In the treatment of our veteran population, the excellent cooperation of practicing physicians has always been a matter of the greatest importance; it is deeply appreciated by the Veterans Administration.

It is interesting to note that over 50 percent of the veterans who are admitted to the West Roxbury Hospital with acute medical or surgical conditions have been referred by practicing physicians. Present regulations, which require veterans to list their assets and liabilities, constitute a safeguard against "chiseling" the Government by signing false statements of inability to defray the necessary expenses of private care.

You may be sure that the professional staffs of both the Veterans Administration Hospitals mentioned above are anxious to work with their colleagues in private practice in giving our veterans the very best possible medical care.

FRANCIS B. CARROLL, M.D.
Area Medical Director
Veterans Administration

Boston

REGARDING "RELIGION AND MEDICINE"

To the Editor: I should like to congratulate you on printing the editorial entitled "Religion and Medicine" in the May 27 issue of the *Journal*. The facts that it sets forth cannot be too strongly stated, and I think it is excellent that they should be presented in a journal of the caliber and large circulation of the *New England Journal of Medicine*.

G. DOUGLAS KRUMBHAAR, M.D.

Boston

BOOK REVIEW

Clinical Roentgenology: Developmental and systemic conditions and local lesions in the extremities. Volume 1. By Alfred A. deLorimier, M.D., Henry G. Moehring, M.D., and John R. Hannan, M.D. 4°, cloth, 492 pp., with 782 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $18.50.

This volume, devoted to the osseous system, is the first in a projected series of four volumes purported to include the entire scope of clinical roentgenology. The contents are divided into developmental malformations, traumatic lesions, metabolic disorders, endocrinopathies, infections, neoplasms and blood dyscrasias. The authors have simplified the diagnostic problem by discussing each condition under the subheadings of general considerations, x-ray manifestations, clinical corroboration, laboratory corroboration and differential considerations. At the end of each section is a very adequate reference to the classic and pertinent articles.

The roentgenologist will find some of the sections on x-ray manifestations too briefly described. Perhaps, in future volumes, these findings will be discussed in fuller detail since, by title, this is primarily a contribution to the roentgenologic literature. However, for review of the clinical and laboratory findings of a given condition this volume is very useful. The work will be well received by the general practitioner, the internist, the orthopedic surgeon and others, for the pertinent features of the diagnostic problem are simply listed.

The x-ray reproductions are very good, and examples—often several projections of each condition—are considered. Again, the roentgenologist will find only the typical and classic illustrations of the process; the variations, the unusual manifestations and the serial comparative studies have not, for the most part, been included. There are many histologic reproductions, which are well correlated. There is a good comprehensive index. This volume is a work of great practical value and can be recommended to anyone interested in roentgenology and its clinical correlation.

SEYMOUR R. SHALEK, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Hunted Heretic: The life and death of Michael Servetus, 1511–1553. By Roland H. Bainton, Ph.D., Titus Street Professor of Ecclesiastical History, Yale University. 8°, cloth, 270 pp., with illustrations. Boston: Beacon Press, 1953. $3.75.

Professor Bainton, in this biography of a noted religious reformer and physician, deals principally with his theologic doctrine. He analyzes the two works on the Trinity and the large book on the restoration of Christianity in which Servetus presented his theory of the circulation of the blood. There are special chapters on Servetus as an editor and a doctor of medicine. The biography is well documented and should be in all medical-history collections.

Clinical Disorders of the Heart Beat. By Samuel Bellet, M.D., director, Division of Cardiology, Philadelphia General Hospital, director, Division of Cardiovascular Diseases, Graduate Hospital, University of Pennsylvania, cardiologist, Einstein Medical Center, associate professor of cardiology and assistant professor of medicine, University of Pennsylvania

School of Medicine, and clinical professor of medicine, Women's Medical College, Philadelphia. 4°, cloth, 373 pp., with 164 illustrations. Philadelphia: Lea and Febiger, 1953. $8.50.

Dr. Bellet treats his subject in four sections: general considerations; individual arrhythmias; arrhythmias in certain clinical states; and drugs used in therapy. Almost two thirds of the text is devoted to a discussion of the individual arrhythmias. There is a bibliography of 496 references and a good index. The book is well published.

The Insight Test: A verbal projective test for personality study. By Helen D. Sargent, Ph.D., senior psychologist, Education Department, Menninger Foundation. With a foreword by Pearl G. Knapp, Ph.D., chief psychologist, Los Angeles Psychiatric Service. 8°, cloth, 276 pp., with illustrations. New York: Grune and Stratton, 1953. $6.75. *(Menninger Clinic Monograph Series No. 10.)*

The Psychopathic Delinquent and Criminal. By George N. Thompson, M.D., associate clinical professor of neurology and psychiatry, University of Southern California School of Medicine, Los Angeles. 8°, cloth, 157 pp., with 16 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $4.50.

Manic-depressive Disease: Clinical and psychiatric significance. By John D. Campbell, M.D., attending psychiatrist, Georgia Baptist Hospital and St. Joseph's Infirmary, Atlanta, chief psychiatrist, Peachtree Sanitarium, Atlanta, and Captain, MC, United States Naval Reserve. 8°, cloth, 403 pp. Philadelphia: J. B. Lippincott Company, 1953. $6.75.

Pregnancy Wastage: Proceedings of a conference sponsored by the Committee on Human Reproduction, National Research Council, in behalf of the National Committee on Maternal Health, Inc. Edited by Earl T. Engle. 8°, cloth, 254 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1953. $8.50.

These proceedings contain 25 articles by authorities in their particular fields. All the aspects of the subject are covered, and there are articles on ACTH and cortisone in pregnancy, and statistics on abortion. The monograph should be in all collections on obstetrics and embryology.

Symposium on Stress. Sponsored jointly by the Division of Medical Sciences, National Research Council, and the Army Medical Service Graduate School, Walter Reed Army Medical Center. 8°, paper, 332 pp., with illustrations and tables. Washington, D.C.: Army Medical Service Graduate School, 1953.

Thirty-seven authorities, who presented papers on various aspects of stress, participated in this symposium. The lack of an index lessens the value of the monograph for reference purposes. The book should be in all collections on the subject.

Essentials of Medical Research. By Wallace Marshall, M.D. 8°, cloth, 176 pp. New York: Vantage Press, Incorporated, 1953. $3.00.

Dr. Marshall has written this book with the idea of acquainting the beginner with the various technics and aspects of medical research. An index would have added to the value of the book.

The Unique Influence of the Johns Hopkins University on American Medicine. By Richard H. Shryock, M.D. 8°, cloth, 77 pp. Copenhagen: Ejnar Munksgaard, Limited, 1953. Kroner 14.-, bound, kr. 17.50.

Dr. Shryock has expanded his address given before the Scottish Society of the History of Medicine in 1950 to present a short account of Johns Hopkins University and its medical school, from its beginnings to the present. A list of 91 historical notes is appended to the text. An index would prove valuable if there should be a reprinting. The publishing is excellent, and the small book should be in all historical collections, medical and general.

The Psychosomatic Concept in Psychoanalysis. Edited by Felix Deutsch, M.D. 8°, cloth, 182 pp. New York: International Universities Press, Incorporated, 1953. $4.00. *(Monograph Series of the Boston Psychoanalytic Society and Institute,* No. 1.)

Five lectures were given in this symposium and 9 physicians discussed the papers. There is an index. The book should be in all collections on psychoanalysis.

Farewell to the Common Cold: An exposition of the body heat theory of Dr. Max Rubner. By Horace Markley. 8°, cloth, 256 pp. New York: Exposition Press, 1953. $3.50.

Mr. Markley discusses the common cold and its prevention by his system of body-temperature control based on Dr. Rubner's postulation. A bibliography of 18 pages concludes the text.

Acute Infectious Hemorrhagic Fevers and Mycotoxicoses in the Union of Soviet Socialist Republics. By D. Carleton Gajdusek, Captain, Medical Corps, United States Army, Department of Virus and Rickettsial Diseases, Army Medical Service Graduate School. 8°, paper, 140 pp., with 7 illustrations. Washington, D. C.: Walter Reed Army Medical Center, 1953. 60c. *(Medical Science Publication* No. 2.)

The author in this monograph has surveyed and summarized the literature on the various types of hemorrhagic fever occurring in the different parts of the U.S.S.R., and also on mycotoxicoses. An appendix presents a survey of nephropathia epidemica in Scandinavia. Lists of references are appended to the chapters. The small book should be in all medical libraries.

Acute Pulmonary Edema. By Mark D. Altschule, M.D., assistant professor of medicine, Harvard Medical School, visiting physician, Beth Israel Hospital, Boston, and director of internal medicine and of research in clinical physiology, McLean Hospital, Waverley, Massachusetts. 8°, cloth, 68 pp. New York: Grune and Stratton, 1954. $3.50. *(Modern Medical Monographs,* No. 10.)

The author has surveyed the pertinent literature on acute pulmonary edema. He divides the text into 4 parts: clinical manifestations; basic physiologic considerations; pathologic physiology; and treatment. There is a bibliography of 93 titles and a good index. This type of monograph should be in all medical libraries.

The Symptoms and Treatment of Acute Poisoning. By G. H. W. Lucas, professor of pharmacology, University of Toronto. 16°, cloth, 308 pp. New York: Macmillan Company, 1953. $4.00.

This valuable manual briefly discusses poisoning in general and its treatment. A list of useful drugs and preparations suitable for emergency treatment occupies 31 pages. The major portion of the text, 193 pages, is given up to a list of poisons, arranged alphabetically. Each poison is described, and its symptoms and treatment indicated. A table of fatal doses is appended to the text. There is an extensive index. The small book is recommended for reference purposes to all physicians and to medical libraries.

Psychological Reflections: An anthology of the writings of C. G. Jung. Selected and edited by Jolande Jacobi. 8°, cloth, 342 pp. New York: Pantheon Books, Incorporated, 1953. $4.50 *(Bollingen Series,* No. 31.)

Dr. Jacobi, long associated with Dr. Jung, has chosen more than 1000 quotations from 60 of the published works and arranged them in a number of categories to illustrate his work in psychology and related subjects. The main parts are the nature and activity of the psyche, man in his relation to others, the world of values and ultimate things. A key to sources is appended to the text. The book was originally published in German and has now been made available in translation for the benefit of English readers. It should be in all collections on psychoanalysis.

Manual of Psychological Medicine for Practitioners and Students. By A. F. Tredgold, M.D., F.R.C.P., F.R.S.E., consulting physician, University College Hospital, London; and R. F. Tredgold, M.A., M.D., D.P.M., physician, Department of Psychological Medicine, University College Hospital, London. Third edition. 8°, cloth, 328 pp. London: Baillière, Tindall and Cox, 1953. $6.00. (Distributed by Williams and Wilkins, Baltimore.)

This standard book was first written in 1943 by the late

Dr. A. F. Tredgold, who is well known for his authoritative textbook, *Mental Deficiency*, which had gone through 8 editions to 1952. This third edition is the joint effort of father and son. The text has been thoroughly revised and brought up to date to include the advances recorded since the printing of the second edition in 1945. The purpose of the work is to introduce psychiatry to the general practitioner and student. The publishing is excellent in every way. The book is recommended for all medical libraries and psychiatric collections.

Einführung in die Lehre vom Adaptationssyndrom. By Hans Selye, Prof. Dr. Med., Dr. rer. nat. (Prag), D.Sc. (McGill), F.R.S. Canada, director, Institut de Médecine et de Chirurgie expérimentales, University of Montreal. Edited and by Prof. Dr. med. Heinz Köbcke, with the collaboration of Dr. med. Rudolf Hoene and Dr. med. Gunnar Heuser. 8°, paper, 164 pp., with 49 illustrations. Stuttgart: Georg Thieme, 1953. DM 16.50. (Distributed by Grune and Stratton, New York.)

This is the German edition of Dr. Selye's book, *The Study of the Adaptation Syndrome*, also translated into French and Japanese.

Dystrophia musculorum progressiva: Eine genetische und klinische Untersuchung der Muskeldystrophien. By Prof. Dr. P. E. Becker, Tuttlingen. 8°, cloth, 311 pp., with 101 illustrations. Stuttgart: Georg Thieme, 1953. DM 28.50 (Distributed by Grune and Stratton, New York.) (Sammlung psychiatrischer und neurologischer Einzeldarstellungen.)

This comprehensive study of progressive muscular dystrophy is based on a large number of cases and on the existing literature of the subject. A genetic study was made of 104 families, showing 175 cases. The cases are given in detail and comprise 145 pages of the text, with a bibliography of 13 pages. The book is a valuable reference source and should be in all medical libraries.

Synopsis of Medical Parasitology. By V. E. Brown, Ph.D., assistant professor of biology, Marquette University. 4°, paper, 109 pp., with 103 illustrations. Milwaukee, Wisconsin: V. E. Brown, 1953. $3.50.

This synopsis is intended for ready reference. It is made up of full-page illustrations, containing 103 figures, with descriptive text. Lists of references are appended to the text and there is an index.

Hygiene des Fusses. By Prof. Dr. F. Schede, director, Orthopädische Universitäts-Klinik a.D., Leipzig, and associate director, Orthopädische Klinik, Sanderbusch, i.O. Seventh edition. 8°, paper, 40 pp. Stuttgart: Georg Thieme, 1953. D.M. 3.60. (Distributed by Grune and Stratton, New York.)

This popular manual on the hygiene of the feet, written by a recognized German authority, deserves translation into English. The text concludes with a series of exercises for the feet, hips and tendons, especially for adults.

NOTICES

NATIONAL SOCIETY FOR CRIPPLED CHILDREN AND ADULTS

The annual convention of the National Society for Crippled Children and Adults will be held at the Hotel Statler, Boston, November 3-5.

AMERICAN COLLEGE OF PHYSICIANS

A course entitled "Newer Developments in Cardiovascular Diseases," under the auspices of the American College of Physicians, will be given at the Mt. Sinai Hospital, New York City, October 11 through 15. The course will be directed by Drs. Arthur M. Master and Charles K. Friedberg.

NEW YORK ACADEMY OF MEDICINE GRADUATE FORTNIGHT

The twenty-seventh annual graduate fortnight of the New York Academy of Medicine will be held at the Academy October 18 through 29. The subject of the meeting will be "Infections and Their Management," and the program will consist of twenty evening lectures, six morning panel meetings, visits to ten hospital clinics and a scientific exhibit. Medical officers of the armed forces, interns and residents will be admitted without charge. Further information may be obtained from the Secretary, Graduate Fortnight, 2 East 103 Street, New York 29, New York.

AMERICAN CANCER SOCIETY GRANTS IN CANCER RESEARCH

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is accepting applications for grants-in-aid for cancer research in the United States. Applications received before October 1 will be considered during the winter and grants recommended will become effective July 1, 1955. Further information may be received from the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D.C.

AMERICAN HEART ASSOCIATION RESEARCH AWARDS

The American Heart Association is accepting applications for research awards; those for research fellowships and established investigatorships may be filed until September 15 and for grants-in-aid until December 1. The awards will be made for studies to be conducted during the year beginning July 1, 1955. The amounts will be as follows: $6000 to $9000 for established investigatorships (1- to 5-year periods subject to annual review); $3500 to $5500 for research fellowships (1- to 2-year periods); and not over $10,000 for grants-in-aid (1- to 3-year periods).

SOCIETY MEETINGS AND CONFERENCES

JULY 6–AUGUST 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1054, issue of June 17.

JULY 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

JULY 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

AUGUST 1–7. Pan-American Congress of Pediatrics. Page 850, issue of May 13.

AUGUST 17–20. Argentine Congress of Thoracic Surgery. Page 708, issue of April 22.

SEPTEMBER 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

SEPTEMBER 6–11. University of Illinois College of Medicine. Annual Assembly in Otolaryngology. Page 1092, issue of June 24.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Washington, D. C.

SEPTEMBER 13–15. American Association of Blood Banks. Page 968, issue of June 3.

SEPTEMBER 22. New England Pediatric Society. Page 968, issue of June 3.

OCTOBER 1 and DECEMBER 3, 1954; FEBRUARY 4 and APRIL 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.

OCTOBER 7 and 8. Pan-Pacific Surgical Association. Page 1092, issue of June 24.

OCTOBER 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.

OCTOBER 11–15. American College of Physicians Course. Notice above.

OCTOBER 16–22. American Occupational Therapy Association. Page 1092, issue of June 24.

OCTOBER 18–29. New York Academy of Medicine Graduate Fortnight. Notice above.

OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

OCTOBER 31–NOVEMBER 4. American Institute of Dental Medicine. Page 968, issue of June 3.

NOVEMBER 3–5. National Society for Crippled Children and Adults. Notice above.

NOVEMBER 12 and 13. Inter-Society Cytology Council. Page 968, issue of June 3.

DECEMBER 5. American Academy of Dental Medicine. Page 1092, issue of June 24.

DECEMBER 8. New England Pediatric Society. Page 968, issue of June 3.

DECEMBER 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.

JUNE 21–25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

(Notices concluded on page xv)